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CONTENTS

PAGE

STUDIES IN THE PATHOLOGY OF RHEUMATIC FEVER. TWO CASES PRESENTING UNUSUAL CARDIOVASCULAR LESIONS 583
(With ten plates)
Alwin M. Pappenheimer and William C. VonGlahn.

MALFORMATIONS OF THE HEART INCLUDING TWO CASES WITH COMMON ATRIOVENTRICULAR CANAL AND SEPTUM DEFECTS AND ONE WITH DEFECT OF THE ATRIAL SEPTUM (COR TRILOCULARE BIVENTRICULOSUM) 595
(With three plates)
Francis D. Gunn and Johanna M. Dieckmann.

A CONGENITAL ANOMALY OF THE HEART: TRUNCUS ARTERIOSUS COMMUNIS 617
(With two plates)
H. M. Zimmerman.

VEGETATIVE ENDOCARDITIS DUE TO THE MENINGOCOCCUS. WITH A CASE REPORT. 623
(With five plates)
C. P. Rhoads.

A CONTRIBUTION TO THE PATHOLOGY OF GENERALIZED ARGYRIA WITH A DISCUSSION OF THE FATE OF SILVER IN THE HUMAN BODY 631
(With eight plates)
A. O. Getler, C. P. Rhoads, and Soma Weiss.

A CASE OF PRIMARY MESENCHYMAL HEPATOMA: WITH NECROPSY . . . 653
(With three plates)
Nathan Chandler Foot.

SARCOSPORIDIAL INFECTION OF THE MYOCARDIUM IN MAN 663
(With one plate)
Samuel W. Lambert, Jr.

A COMPARISON IN NORMAL, THYROIDECTOMIZED AND HYPOPHYSECTOMIZED RATS OF THE EFFECTS UPON METABOLISM AND GROWTH RESULTING FROM DAILY INJECTIONS OF SMALL AMOUNTS OF THYROID EXTRACT 669
Philip E. Smith, C. F. Greenwood, and G. L. Foster.

INDEX OF SUBJECTS 689

INDEX OF AUTHORS 701

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THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME III NOVEMBER, 1927 NUMBER 6

STUDIES IN THE PATHOLOGY OF RHEUMATIC FEVER*

TWO CASES PRESENTING UNUSUAL CARDIOVASCULAR LESIONS

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The more closely one studies material from cases of rheumatic disease the more does it become apparent that the lesions of the vascular system are more diverse and more widely distributed than is generally supposed. The cases here reported illustrate this point and add several new observations to previous descriptions of the pathology of rheumatism. These new features of interest are, in brief, an aortitis with peculiar characteristics not heretofore described and a specific type of panarteritis affecting the larger arteries (coronaries, renal, superior mesenteric and coeliac axis). The absence of complicating lesions and infections, the youth of the patients and the typical clinical courses add significance to the findings.

CASE I

F. L. (History 62760, Necropsy 9867), white male, age 15 years.
Family History. Irrelevant.
Past History. Negative.
Present Illness: Onset in 1922 with an attack of sore throat, followed after a week by swollen, painful, tender joints of lower extremities and hands. During the next two years he had eight to ten similar attacks of polyarthritis, usually preceded by sore throat. In 1923 he began to have dyspnea, orthopnea and palpitation.

He was first admitted to the Presbyterian Hospital in April, 1925, complaining of swollen, red and painful joints, shortness of breath and fever which had continued for one month. At this time his temperature was 103.6° F; he was somewhat cyanotic and definitely orthopneic. His heart was greatly enlarged, the left border reaching to the axilla. The heart rate was rapid. At the

* Received for publication July 15, 1927.

apex and base systolic and diastolic murmurs were heard. The pulse was of the Corrigan type. The knees, ankles and wrists were somewhat tender and red. Tonsils were enlarged. White blood cells, 7,600, polymorphonuclears 54 per cent. Blood cultures on three occasions remained sterile. The tonsils were removed. He was kept in the hospital for four months.

In October, 1926, he returned complaining of cough and pain in the right chest, chills, fever and headache. His temperature was 104° F. The heart condition had not changed. He was found to have lobar pneumonia, involving the right lower lobe. The consolidation later spread to the right middle and left lower lobes. Blood culture showed no growth of organisms. The white blood cell count of 9,500 with 84 per cent polymorphonuclears on admission increased to 25,000 with 92 per cent polymorphonuclears. During the course of the pneumonia he had pus in his urine. Pneumococcus Type II was recovered from the sputum culture.

About two weeks after entrance an acute infection developed in the left parotid gland which later required incision and drainage. From the gland *staphylococcus aureus* was isolated. Blood cultures after the onset of the acute parotitis remained sterile. The white blood count rose to 30,000 with 90 per cent polymorphonuclears. Following the incision of the gland, the white blood cells quickly dropped to 9,200. The pneumonia, and the parotitis cleared up satisfactorily and when he was discharged from the hospital at the end of two months he showed no signs of cardiac decompensation.

In January, 1927, he came to the emergency ward complaining of pain in both flanks. No cause for this pain could be discovered. At this time he also had acute pharyngitis.

Three weeks later he again returned because of a "pounding" pain in the chest and abdomen, unrelated to respiration. He again had acute pharyngitis. He was admitted to the hospital. The heart condition had not changed. A single petechia was discovered in the conjunctiva of the right eye. The fingers were not clubbed. The lower border of the liver was 3 cm. below the costal margin. The spleen could not be palpated. The white blood cells numbered 9,100 with 65 per cent polymorphonuclears.

The pain became localized to the precordial region; a pericardial friction rub became evident ten days after he entered the hospital, and at about the same time he had an attack of polyarthritis. The white blood count rose to 28,000 with 86 per cent polymorphonuclears. His temperature frequently reached 103° F.

Blood cultures were made on three occasions. Two of the cultures were incubated for four weeks, the other for six weeks. No growth occurred in any of them. He died thirteen days after entrance in the hospital.

Heart

Gross Examination: The heart is greatly enlarged, weighing with a portion of the pericardial sac, 740 gm. The parietal pericardium over several areas is bound by dense adhesions to the heart. Elsewhere the pericardial surfaces are covered with a thick, shaggy, fibrinous exudate. All chambers are enlarged. The right and left ventricles are hypertrophied. Along the line of closure of the septal

and infundibular leaflets of the tricuspid valve are small areas of roughening. The pulmonic valves are normal. In the left auricle, the endocardium above the posterior leaflet of the mitral valve presents ridges and furrows; these run roughly perpendicular to the valve ring and extend also to the orifice of the auricular appendage. The area so involved is 8 × 5 cm. Both leaflets of the mitral valve are thickened and are fused together so that the opening measures only 5.2 cm. On the posterior leaflet along the margin in two places are several small yellowish grey, tough vegetations. The chordae tendineae are markedly thickened. The endocardium of the left ventricle has numerous yellow flecks in it. Near the apex of the posterior papillary muscle is an endothelial pocket pointing upward toward the auricle. Below the anterior and left posterior aortic leaflets the endocardium is thrown up into folds, one of which forms a small pocket, directed toward the apex. The aortic leaflets are thickened. The free border of the right posterior leaflet of the valve is rolled toward the sinus side. There is some fusion between the anterior and right posterior leaflets. Small yellowish grey vegetations are present on the free margin of the right posterior leaflet. The myocardial fibers are coarse. There is no apparent scarring.

Microscopic Examination: The histologic structure of the vegetations on the mitral and aortic valves is that characteristic of rheumatic verrucae — hyaline, eosin-staining masses, into the base of which large fibroblast-like cells are growing (Fig. 1). There is no polymorphonuclear reaction, and no bacteria are found. The valve is greatly thickened, vascularized, and contains occasional mononuclears and eosinophiles and a few imperfectly formed Aschoff bodies surrounding areas of fragmentation and swelling of the collagen (Fig. 2).

The myocardial lesions are intense and characteristic. Throughout all the blocks examined, one sees typical lesions in the vicinity of small branches of the coronary arteries (Fig. 3). Since these present all the well-known features of Aschoff lesions, they need not be described in detail. The fibrinous pericarditis is shown in Fig. 4.

The auricular lesions conform in their histologic details to the descriptions given by MacCallum [1] and by VonGlahn [2] in previous papers. They may be summarized as consisting of band-like necroses of collagen about which are palisades of basophilic-staining cells, collections of distorted and fragmented nuclei, with eosino-

philes and polymorphonuclear neutrophiles, often localized to certain areas in the greatly thickened endocardium (Fig. 5).

On the surface, the single row of flattened cells has been supplanted in many places by a peculiar new tissue, which merits more detailed description, since the same sort of tissue is found lining many of the peripheral vessels. The cytologic composition of this tissue is difficult to analyze. It consists of spindle-shaped cells directed for the most part perpendicularly to the surface. Their nuclei are pycnotic, elongated, often somewhat angular, or drawn out into strands of odd shape. The outlines of individual cells are indefinite. The groundwork is formed by an indistinct fibrillar material, and by the basophilic cytoplasm of the large cells. In the interstices are leucocytes, both polymorphonuclear and occasionally eosinophiles. Many of the nuclei are too distorted to be readily identified (Fig. 6).

The relation to the elastic fibers is somewhat variable. The fibers may be found on either side of this new tissue, and fine fibrillae, often cut in cross-section, run between the individual cells (Fig. 7).

The tissue does not always lie upon the surface, but may be covered by a stratum of fibro-elastic tissue running parallel to the surface.

Very interesting lesions are present also in the endocardium of the left ventricle. In places these have the usual structure and arrangement of Aschoff nodules. Thus Fig. 8 shows a rosette of Aschoff cells disposed about a mass of necrotic collagen. But a more diffuse reaction is found over large areas of endocardium (Figs. 9 and 10). Dense collections of nuclei belonging to polymorphonuclears, lymphoid cells, large mononuclears with vesicular nuclei (endotheliocytes?) and other nuclei which cannot be identified because of their distorted shape and pycnotic staining, occupy the loose fibro-elastic tissue of the endocardium and project irregularly upon the surface. There is no thrombus or vegetation superimposed; the overlying endothelium is intact in some places, but in others it is lost. The cells taking part in this reaction are identical with those in the auricular endocardium, although their arrangement is slightly different. These infiltrations were the cause of the yellow flecks seen in the ventricular endocardium.

Aorta

In previous papers dealing with rheumatic aortitis, Klotz [3] and the writers [4] described lesions which followed the distribution of the vasa vasorum into the outer portion of the media. The present case shows abundant lesions of this sort (Fig. 11). But there is, in addition, a pathologic process easily differentiated from the common form of atherosclerosis, which affects predominantly the *intima* and the *subjacent portions of the media*. The rheumatic origin of these lesions will become clear from the analogies to the changes in the auricular endocardium.

Gross Examination: The aorta has the appearance illustrated in Fig. 12. In each of the sinuses of Valsalva are small ridges or plaques in the intima. These are pale brownish in color, glistening and translucent. Above the junction of the anterior and left posterior leaflets of the aortic valve is a larger similar plaque which reaches to the orifice of the left coronary artery. Above the anterior and right posterior aortic leaflets, and separated from them by apparently normal aorta, is a brownish, translucent intimal plaque having a delicately ridged surface as though small areas had become confluent. In nearby portions of the intima are several small, rounded, or oval areas of similar appearance.

Near the margin of the large plaque are a number of narrow atheromatous streaks; these are opaque, orange-yellow and dull.

The pale brown elevations are very similar in appearance to the lesion of acute rheumatic auricular endocarditis, and are in sharp contrast with the dull opaque orange-yellow atheromatous lesion, and the grey glistening wrinkled plaque of syphilitic aortitis.

Because of the restrictions imposed upon the necropsy, the remainder of the thoracic aorta was not removed. In the abdominal portion are a few characteristic atheromatous streaks. Near the bifurcation the wall of the aorta seems distinctly thickened as compared with the vessel wall in the region of the diaphragm.

Microscopic Examination: The microscopic changes affect all the elements of the intima, and in many places the subjacent media.

A block was taken through a translucent plaque shown at the upper cut edge of the ascending aorta. Here are found bands of non-nucleated fibrillar material in the intima, bordered by rows of deeply staining cells with basophilic cytoplasm and one or occasion-

ally two large vesicular nuclei containing a central dense clump of chromatin (Figs. 13 and 14). In their arrangement and staining reaction, these cells are identical with those so characteristically present in the auricle. Where these cells are more sparsely arranged, they assume very irregular shapes. The nucleus is often lobate or bent upon itself, and long plasmatic processes can be traced from the cell body into the crevices of the fibrillar matrix.

The medial lesions in the areas below the intimal plaques are diffuse, but definite. They are best brought out in sections prepared by the Weigert-Van Gieson methods. Perhaps the most striking change is complete loss of muscle cells over large areas, so that only the collagen and elastic fibers persist. This change is foreshadowed in the hematoxylin-eosin preparations in which the muscle nuclei in the corresponding areas have largely disappeared. The elastic fibers are thinner, less wavy and less well stained than in the better preserved regions of the media. In places there is actual rupture or fragmentation.

Toward the outer third of the media are encountered perivascular lesions which are like those described in previous papers. They are unusually numerous and many of the cells found in the vicinity of the nutrient vessels have as definitely the character of "Aschoff cells" as in any case which we have studied (Fig. 11).

Blocks taken through the large plaques above the aortic leaflets bring out certain additional features. The intimal plaque itself is composed of a rather loose tissue made up of irregular cells tending to a vertical orientation and separated by an indefinite fibrillar stroma. At the margin of the plaque, the endothelium, which in the normal portion of the aortic wall consists of a flattened layer of single cells, becomes dissociated; the individual cells assume a polyhedral form and appear to migrate into the subjacent stroma. Occasionally clefts containing red blood cells are bordered by such polyhedral cells (Figs. 15 and 16). In certain sections, the clefts appear to communicate with the lumen of the vessel.

This peculiar tissue resembles in no wise the tissue which composes the ordinary atheromatous plaque. Sections stained with Scharlach R show only occasional cells containing finely divided fat, which with the polarizing microscope is not anisotropic. There are no free lipoid masses, no large foamy fat-containing cells and no cholesterin crystals. One interesting field is illustrated in Fig. 17.

Here the internal elastic lamella is split into two distinct layers; the upper one is intact, lying immediately beneath the stratum of intimal tissue described. The lower lamina in places is interrupted by patches of scar tissue, about which are grouped irregular vertically disposed cells. This gives indisputable proof of the cicatricial character of these intimal lesions.

The adventitia is very greatly thickened in all blocks examined, and particularly in those taken from the ascending arch in the region of the plaques, and from the lower abdominal aorta. The nutrient arteries have thick walls; the different coats are not easily distinguished. The lumen is often narrowed (Fig. 18) and in some of the large vessels lined with a layer of new tissue closely resembling that in the intima of the aorta. The elastic fibers are frayed and reduplicated and the muscle fibers are separated by connective tissue and young fibroblasts.

In one nutrient vessel in the abdominal portion, there is a focal collection of large cells resembling an Aschoff nodule (Fig. 19).

Coronary Vessels

1. A block was taken through the beginning of the left coronary artery close to its orifice. The changes are similar to those seen in the aortic plaque; the intima is represented by a loose tissue which appears to be derived from the endothelium itself, together with a few wandering cells, including a fair number of polymorphonuclears (Fig. 20).

2. A large branch of a coronary artery shows an elevated parietal thrombus projecting into the lumen. This is composed of a mass of fibrin, the filaments of which run vertically. Entangled in the fibrinous net are numerous deeply stained nuclei, many of which appear to belong to polymorphonuclears. A few leucocytes are seen between the muscle fibers beneath the thrombus (Figs. 21 and 22).

3. A lesion is present about a small capillary which resembles that described and pictured in a previous paper.[5] The vessel over a small area is surrounded by a mass of fibrin which infiltrates the surrounding tissue. At the margin of the fibrin there are many Aschoff cells and a few polymorphonuclear leucocytes. The lumen is not occluded by thrombus and the endothelium is intact (Fig. 23).

4. A vein is cut longitudinally. One side of the wall shows a normal structure; the other is lifted up into irregular prominences by a

mass of infiltrating cells, which have replaced the muscular elements and pushed up the intact overlying endothelium into the lumen. The appearance of this lesion is shown in Figs. 24 and 25.

Coeliac Axis and Superior Mesenteric Arteries

It was discovered in the fixed specimens of duodenum and pancreas that both these arterial trunks were very greatly thickened. The lumen was much reduced in diameter and in the case of the superior mesenteric artery, it appears in the form of a tortuous cleft because of the presence of new tissue in the intima (Fig. 26). The walls are creamy white and very greatly thickened in comparison with those of a normal vessel cut in the same situation in another individual of about the same age.

Microscopically, all the coats are affected by an inflammatory and productive reaction of great intensity but presenting certain features which correlate the lesions with those found in other portions of the cardiovascular system.

The intima is much thickened by the new formation of a loose fibrocellular tissue. The overlying endothelium is preserved. In places the superficial areas are quite cellular and the arrangement and morphology of the cells resemble that in the new tissue covering the aortic plaques. In other areas the cells are few and far apart, being separated by a pink, more or less hyalinized ground substance.

The internal elastic lamella is highly irregular, being split into numerous laminae, some of which lie in the superficial portion of the plaque, just over the new tissue above described; other laminae lie between the intimal plaque and the media. The area in which the cells are sparse and the ground substance more or less hyalinized contains virtually no elastic fibers. Elsewhere in addition to the circumferentially disposed lamellae, there are numerous delicate fibrils running in all directions. In several areas just internal to the innermost layer of the internal elastic lamella, these cellular foci are composed largely of distorted polymorphonuclear cells (Fig. 27).

The chief lesion in the media consists in the presence of polymorphonuclears, scattered individually between the muscle fibers, but occasionally forming more compact aggregates (Fig. 28). In some areas, there is a local loss of muscle nuclei, their place being taken by a fine fibrillar ground substance. The muscle nuclei, especially

those in the vicinity of these rarefied areas, are distorted and vesicular rather than rod-shaped.

The adventitia is represented by dense collagenous connective tissue radiating into the surrounding fat. Between the bundles of fibers are numerous capillaries characterized by very swollen endothelium, almost occluding the lumen. In addition there are many small lymphoid cells, polymorphonuclears and large mononuclears with basophilic cytoplasm and processes extending into the crevices of the tissue (Fig. 29).

Frozen sections stained with Scharlach R show only a few cells in the intima containing finely divided fat. As in the other lesions, this is not anisotropic.

Renal Artery

In one of the branches an early intimal lesion of similar nature is encountered (Fig. 30).

Case II

We have found in our material another clearcut example of this type of aortic involvement.

The case was that of a negro boy, age 14 (History 60354, Necropsy 9529) who had had frequent attacks of sore throat until his tonsils were removed, but never polyarthritis. A year before entering the hospital he had an attack of precordial pain, dyspnea and fever, following which he was short of breath on exertion. Three weeks before admission he began to have substernal pain which spread to the precordium. Later he had fever and sweats, and became very dyspneic and orthopneic. For four days his feet had been swollen. At the apex of the heart a presystolic and a systolic murmur were heard; at the base a diastolic murmur was present. His pulse was collapsing. He died four days after entering the hospital.

The pericardial sac is everywhere bound to the heart by fibrous adhesions. Typical verrucae are present on the tricuspid, mitral and aortic valves. The left auricle presents the characteristic picture of rheumatic involvement of the endocardium, and the case has been reported in that connection (Case VI).[2] In the myocardium are numerous Aschoff bodies.

The aorta grossly shows only what appears to be early atheroma in the form of narrow orange colored streaks along the posterior wall of the descending thoracic and abdominal portions.

A section taken from the midthoracic portion shows two lesions, differing somewhat from one another but preserving the now familiar features as seen in the auricle. One of these is shown in Figs. 31 and

32. Beneath a small atheromatous plaque composed of large lipoid-containing cells, with a few smaller lymphoid elements, are seen rows of large polyhedral basophilic cells, vertically directed about bands of non-nucleated fibrillar material. The other lesion does not lie beneath an atheromatous plaque. The deeper portion of the intima and the subjacent media are occupied by dense accumulations of cells of two types: (1) large polyhedral elements with vesicular nuclei, like those in the other lesion and (2) deeply staining nuclei, some of which obviously belong to polymorphonuclears; others are distorted beyond recognition, the chromatin being drawn out into threads with bulbous ends (Figs. 33 and 34). This combination is exactly like that so characteristically found in the auricular lesions, as may be seen in Fig. 5.

In the superior mesenteric artery of this case, studied in the fixed museum specimen, there are seen with the stereoscopic microscope gelatinous reddish elevations projecting into the lumen. Sections from these areas show lesions of the intima like those noted in the previous case. The most striking feature is the presence of the distorted, deeply staining nuclei in a zone which includes the intima and the media immediately outside of the internal elastic lamella. Some of these nuclei are derived from migrating polymorphonuclear leucocytes since similar cells in the auricular lesion have been found to give the oxidase reaction; others, however (those which are more elongate), appear to belong to large mononuclear wandering cells as they show no oxidase granules. The lesions are not present throughout the circumference; in some fields, the intimal tissue shows a normal structure. The internal elastic lamella is split into two or several layers and is swollen. A few leucocytes with distorted nuclei may be found in all portions of the media. The adventitia is free from striking changes. A few loose perivascular lymphoid accumulations are present.

Conclusions

It has not been thought necessary to review again the literature dealing with rheumatic vascular disease, since this has been adequately covered in previous papers and in the recent admirable summary by Sacks.[6]

We have found a few references to the occurrence of verrucous lesions on the intima of the aorta and, in one instance (Heydloff[7]),

in the innominate and carotid arteries. In one of the best described cases, that of Barbacci,[8] these lesions began 1 cm. above the sinus of Valsalva and histologically were not unlike the organizing verrucae of rheumatic endocarditis. Bacteria could not be demonstrated in them. The heart was normal.

It is quite possible that some of the cases were rheumatic in origin though no reference is made to this possibility by the authors. Neither are the histologic descriptions sufficiently detailed to justify any definite conclusions. It must be remembered, however, that these papers antedated the recognition of the specificity of the lesions in rheumatic cardiac disease.

While many of the older writers, and particularly French authors, have ascribed to the "rheumatic virus" an important place in the causation of arterial disease, the connection was based upon clinical inference rather than histologic specificity. The recent studies upon the auricular lesions have made it apparent that the rheumatic infection may be evidenced by a diffuse response as distinctive in its cellular composition and arrangement as is the Aschoff nodule or the endocardial verruca.

It is therefore not surprising that one may find this specific type of reaction not confined to the heart, but taking place also in the lining of the aorta and the larger arteries. The detailed study of these cases brings evidence of this fact. Such evidence is of necessity indirect and based chiefly upon the analogy of the lesions in the blood vessels with those admittedly of rheumatic origin occurring in the auricular endocardium. Until the specific agent shall have been finally identified and similar lesions experimentally produced, this is as far as one can go.

The lesions which have been depicted in the aorta are, in these cases, not mere extensions from the aortic valves, since they occurred at a distance, indeed in the second case, in the midthoracic portion. The aortitis is of two types, which may be associated or occur discretely, and which probably corresponds to the route of infection. When this takes place from the lumen, there is produced a diffuse reaction in the intima and subjacent media, comparable to that which so frequently affects the auricular endocardium. On the other hand, infection reaching the aortic wall via the vasa vasorum produces a focal perivascular reaction, more closely analogous to the Aschoff nodules about the small branches of the coronary vessels.

It is not maintained that this difference in type of reaction is of fundamental importance; it may be in part dependent upon the peculiarities of the structural arrangement of the tissue in which the reaction is occurring.

It seems to us, however, of importance to recognize the fact that the pathology of rheumatic infection does not begin and end with the Aschoff nodule. Experience has taught us to recognize as equally distinctive the more diffuse reaction whether it occur in the valves, endocardium, aorta or the smaller visceral vessels.

We are indebted to Dr. Walter W. Palmer for permission to transcribe the clinical records, and to Mr. Alfred Feinberg for the drawing.

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DESCRIPTION OF PLATES

PLATE 146

FIG. 1. Necropsy 9867. Rheumatic endocarditis of aortic valve. (H. and E. stain.)

FIG. 2. Necropsy 9867. Aortic valve: Necrosis of collagen with beginning accumulation of Aschoff cells. (H. and E. stain.)

FIG. 3. Necropsy 9867. Aschoff body in myocardium. (H. and E. stain.)

FIG. 4. Necropsy 9867. Rheumatic pericarditis. Exudate of fibrin with hemorrhage and early organization.

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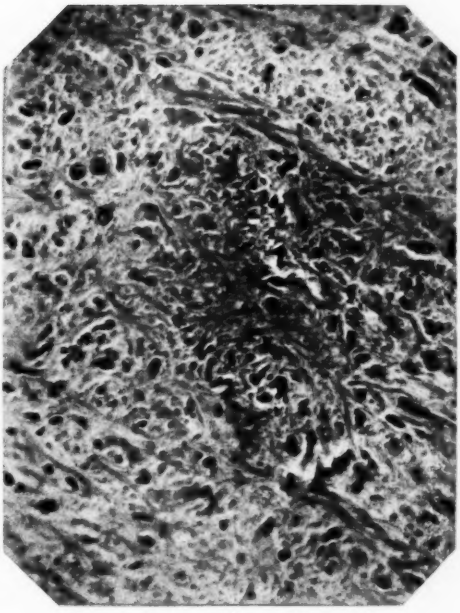

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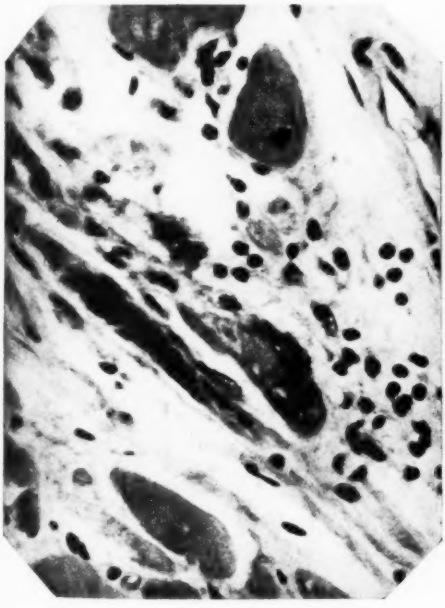

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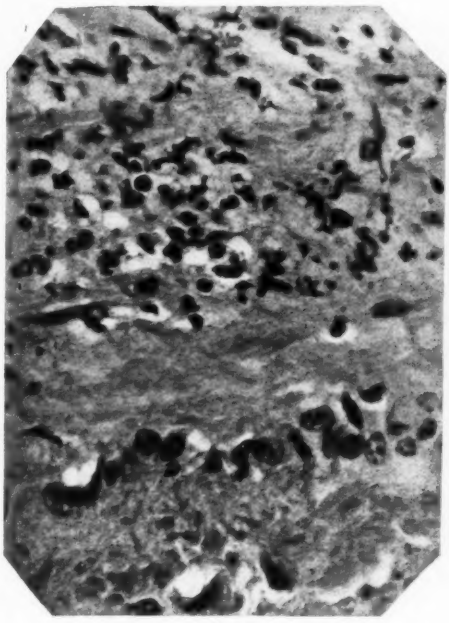
Pappenheimer and VonGlahn Pathology of Rheumatic Fever

PLATE 147

FIG. 5. Necropsy 9867. Acute rheumatic endocarditis of left auricle. Band of necrotic collagen with palisade of basophilic cells on one side; on the other side, a collection of cells, consisting of polymorphonuclear neutrophiles, eosinophiles, and cells with distorted nuclei. (H. and E. stain.)

FIG. 6. Necropsy 9867. Rheumatic endocarditis of left auricle. New tissue composed of cells directed perpendicularly to surface, polymorphonuclear leucocytes and spindle cells. Nuclei of cells distorted and pycnotic. The new tissue penetrates through gaps in the elastic fibers. (H. and E. stain.)

FIG. 7. Necropsy 9867. Rheumatic endocarditis of left auricle. Consecutive sections. Photographs of corresponding fields. (A) Layer of new tissue composed of cells as described in Fig. 6. (H. and E. stain.) (B) The new tissue lies internal to the elastic fibers. (Elastic tissue and Van Gieson stain.)



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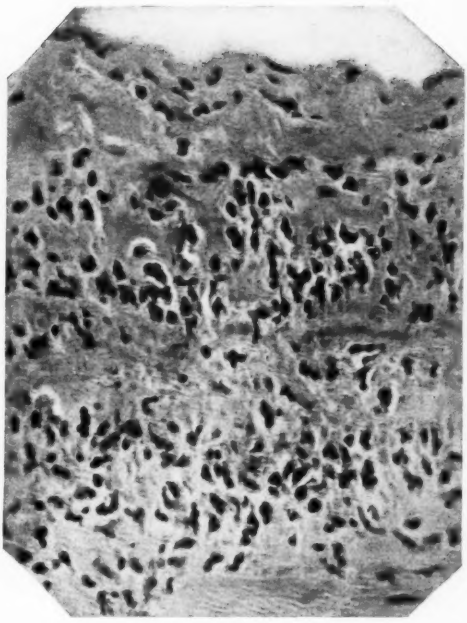

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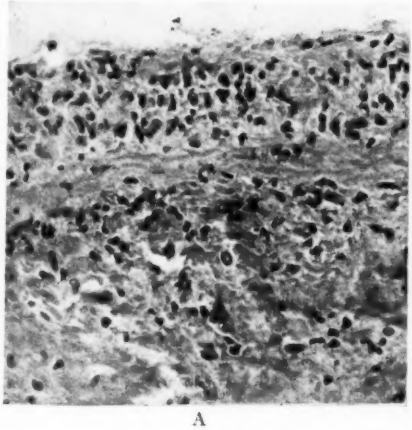

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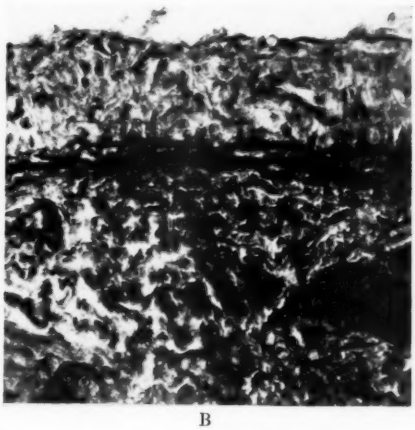

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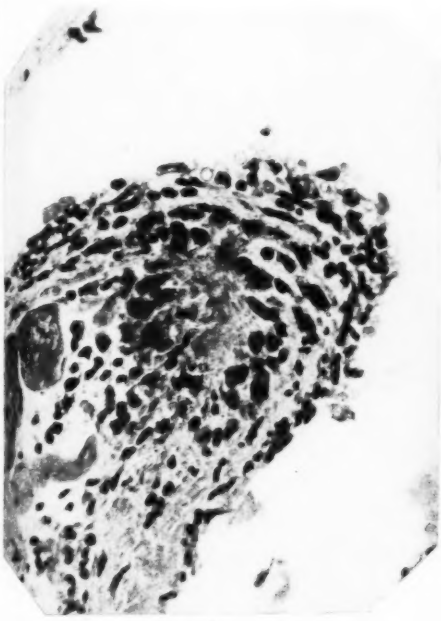
PLATE 148

FIG. 8. Necropsy 9867. Aschoff body in endocardium of left ventricle. (H. and E. stain.)

FIG. 9. Necropsy 9867. Rheumatic endocarditis of left ventricle. Acute diffuse reaction. Many polymorphonuclears, lymphoid cells, and large mononuclear cells. (H. and E. stain.)

FIG. 10. Same as Fig. 9. High power.

FIG. 11. Necropsy 9867. Rheumatic aortitis. Collection of cells about penetrating vessel in media. Some of the cells are small mononuclears, others are typical Aschoff cells. (H. and E. stain.)



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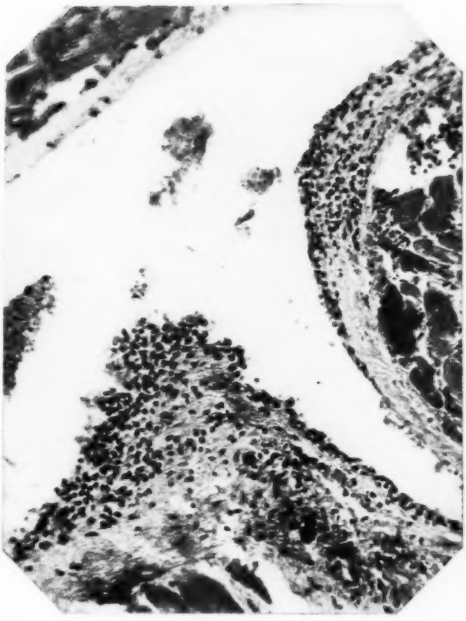

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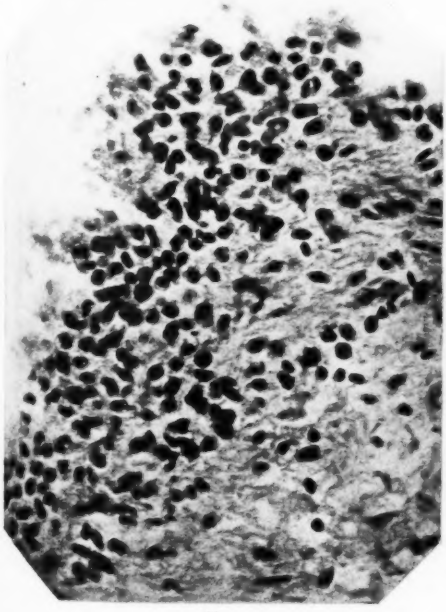

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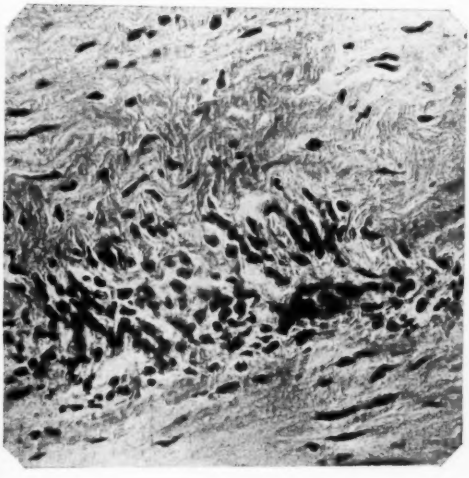

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Pappenheimer and VonGlahn Pathology of Rheumatic Fever

PLATE 149

FIG. 12. Necropsy 9867. Rheumatic aortitis. Translucent pale brown plaques in intima in sharp contrast to atheromatous streaks nearby. Rheumatic endocarditis of aortic valve. Thickening of ventricular endocardium beneath aortic valve. Anterior leaflet of mitral valve and chordae tendineae thickened. Rheumatic pericarditis.

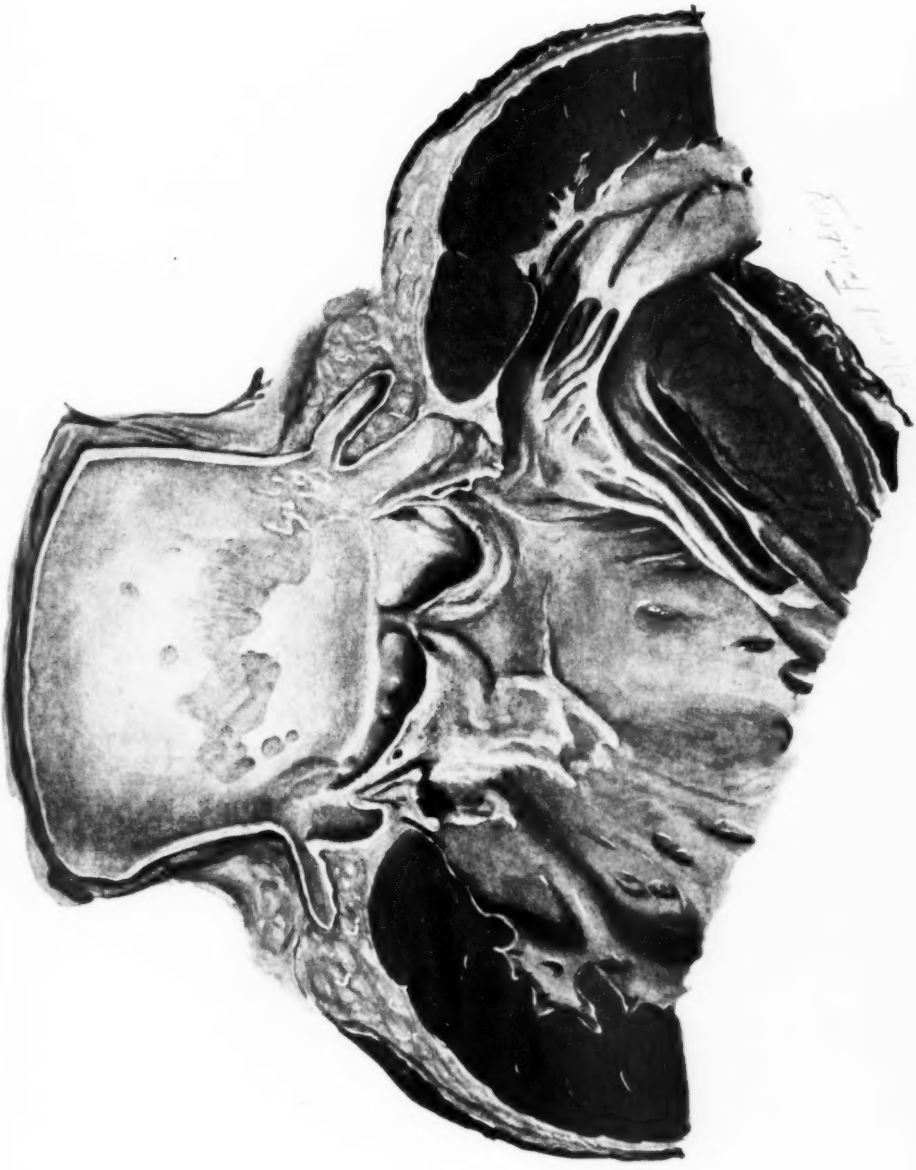

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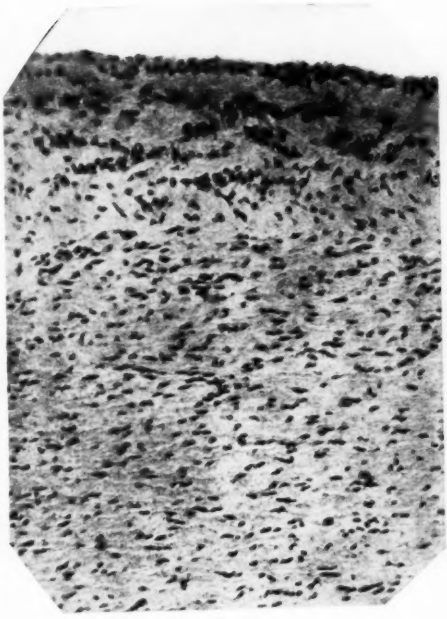
PLATE 150

FIG. 13. Necropsy 9867. Rheumatic aortitis. Bands of non-nucleated fibrillar material in the intima, bordered by rows of cells with basophilic cytoplasm. (H. and E. stain.)

FIG. 14. Same as Fig. 13, high power.

FIG. 15. Necropsy 9867. Rheumatic aortitis. Consecutive sections. Photographs of corresponding fields. (A) Intimal plaque composed of loose tissue made up of irregular cells separated by fibrillar stroma. Small clefts in the new tissue. In the adjacent media, most of the nuclei have disappeared. (H. and E. stain.) (B) The intimal plaque is internal to the elastica interna. Rupture and fragmentation of the elastic fibers in adjacent part of media. (Elastic tissue and Van Gieson stain.)



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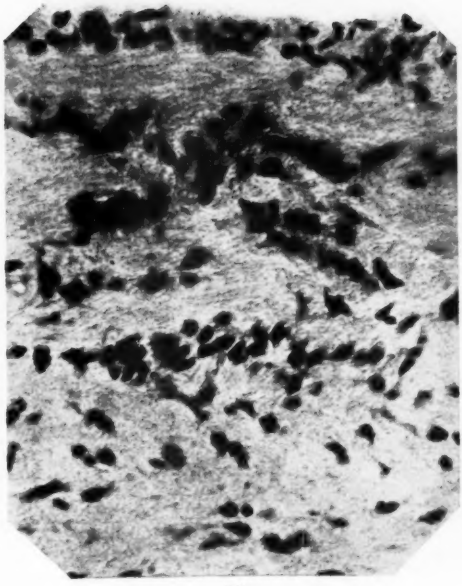

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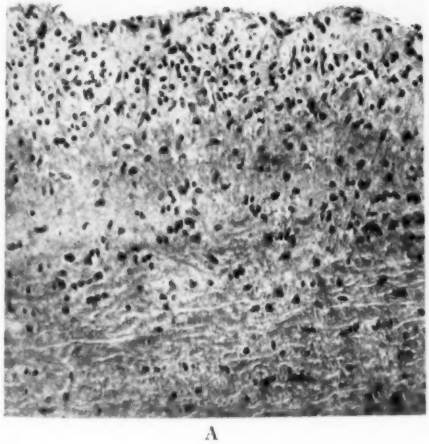

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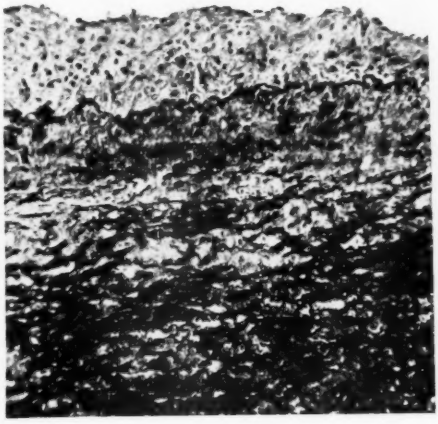

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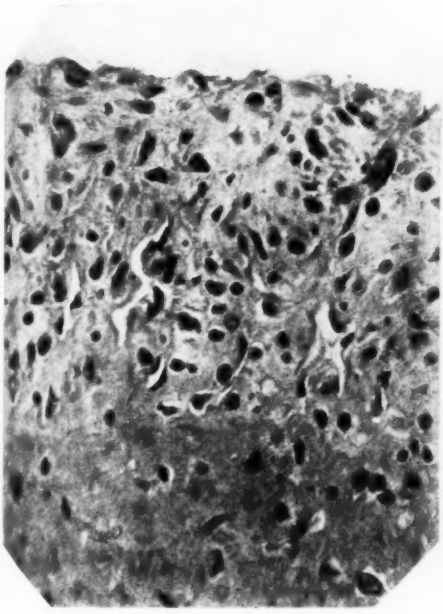
Pappenheimer and VonGlahn Pathology of Rheumatic Fever

PLATE 151

FIG. 16. Rheumatic aortitis. High power of a field of Fig. 15, A.

FIG. 17. Necropsy 9867. Rheumatic aortitis. Layer of new tissue as described in Fig. 15; internal elastic lamella split into two layers. The inner layer is intact and lies immediately beneath the new tissue; the outer layer is interrupted by patches of scar tissue. (Elastic tissue and Van Gieson stain.)

FIG. 18. Necropsy 9867. Rheumatic aortitis. Great thickening of adventitia. Nutrient artery thick-walled and lumen narrowed. Thoracic aorta. (H. and E. stain.)



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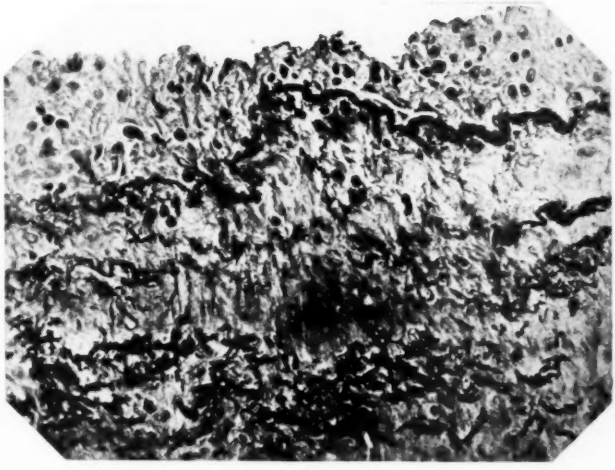

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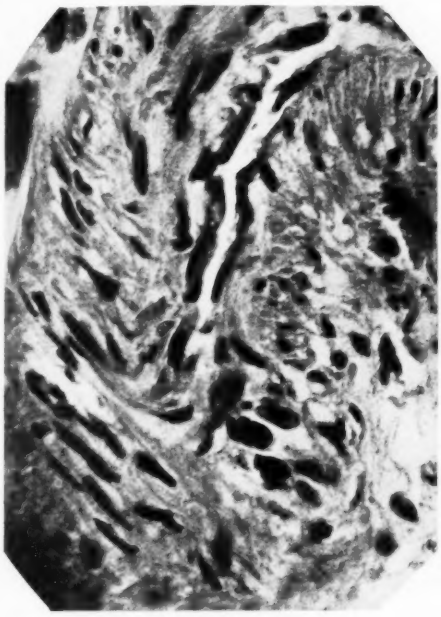
PLATE 152

FIG. 19. Necropsy 9867. Section from abdominal aorta. Nutrient vessel with focal collection of large cells in its wall. One of the cells contains two nuclei. (H. and E. stain.)

FIG. 20. Necropsy 9867. Left coronary artery. New tissue in intima, apparently derived from the endothelium together with few wandering cells and polymorphonuclears. (H. and E. stain.)

FIG. 21. Necropsy 9867. Coronary artery. Parietal thrombus. (H. and E. stain.)

FIG. 22. Same as Fig. 21, high power.



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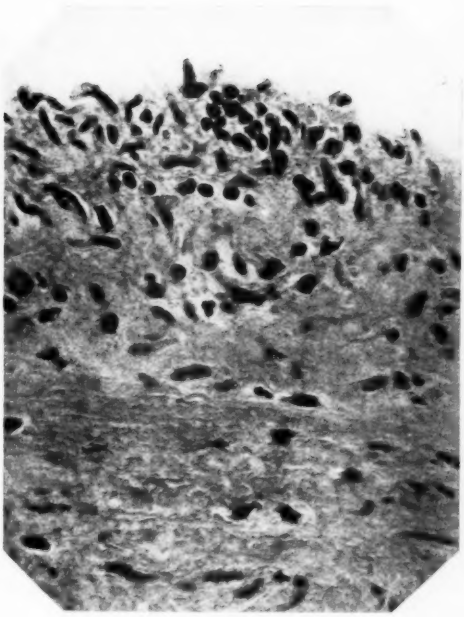

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Pappenheimer and VonGlahn Pathology of Rheumatic Fever

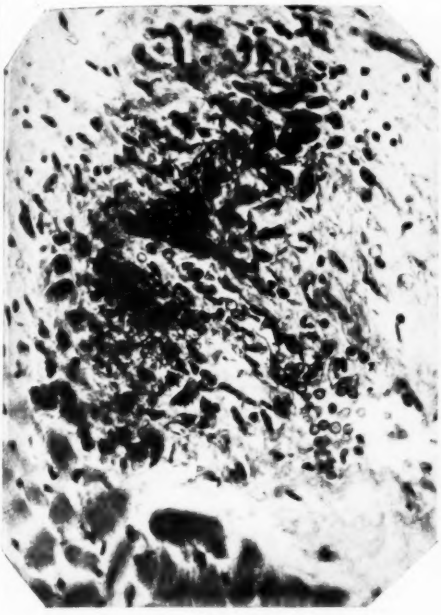
PLATE 153

FIG. 23. Necropsy 9867. Capillary in myocardium. Fibrin on either side of vessel, with Aschoff cells and polymorphonuclears. Lumen of capillary not occluded by a thrombus. (H. and E. stain.)

FIG. 24. Necropsy 9867. Vein in myocardium. Vessel wall infiltrated with polymorphonuclears and large basophilic mononuclear cells; a few cells have distorted nuclei. Endothelium swollen but intact. (H. and E. stain.)

FIG. 25. Same as Fig. 24, high power.

Fig. 26. Necropsy 9867. Superior mesenteric artery. Thickening of adventitia and intima. Lumen narrowed. (Elastic tissue and Van Gieson stain.)



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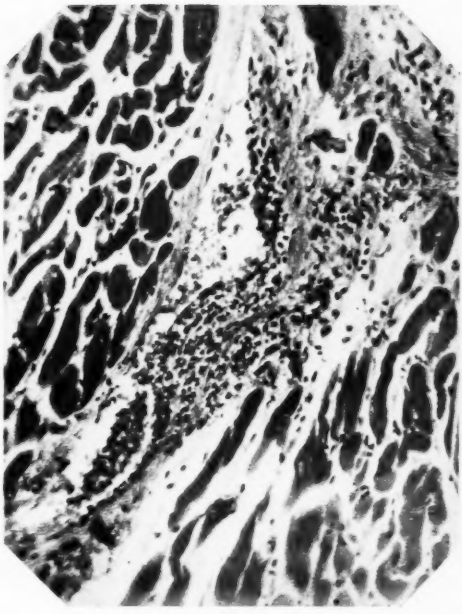

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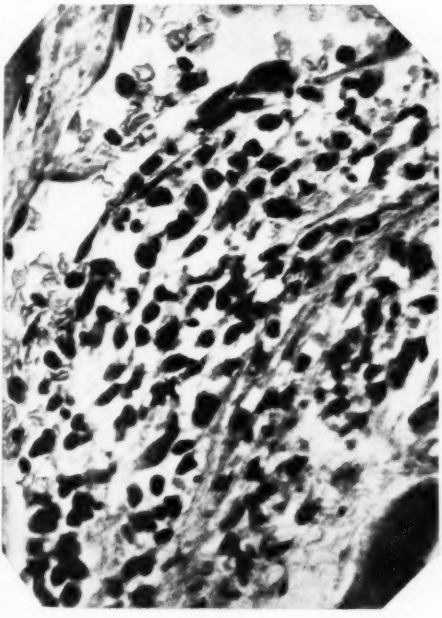

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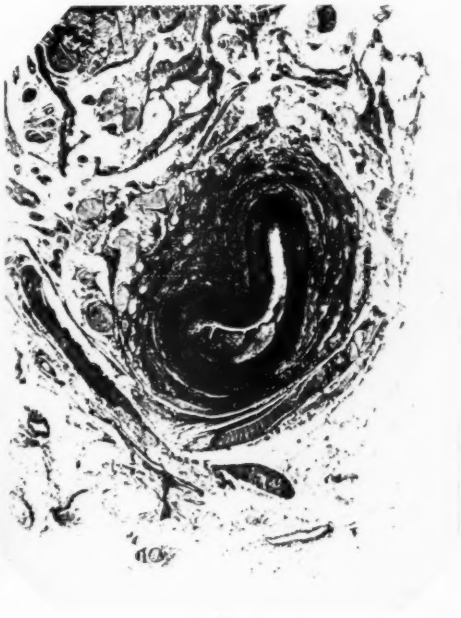

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Pappenheimer and VonGlahn Pathology of Rheumatic Fever

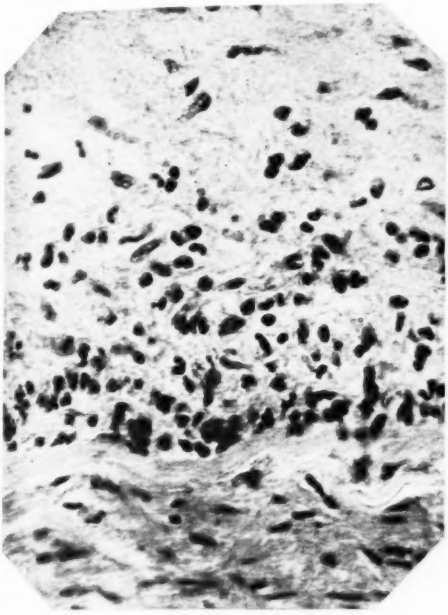
PLATE 154

FIG. 27. Necropsy 9867. Coeliac axis. Intima thickened by a loose fibrocellular tissue. Accumulation of polymorphonuclear leucocytes internal to the elastic interna. Many of the leucocytes have distorted nuclei. (H. and E. stain.)

FIG. 28. Necropsy 9867. Coeliac axis. Infiltration of media with polymorphonuclears. (H. and E. stain.)

FIG. 29. Necropsy 9867. Coeliac axis. Polymorphonuclear infiltration of media. Adventitia thickened by dense collagenous connective tissue, in which are capillaries, small lymphoid cells, polymorphonuclears, and large mononuclear cells. (H. and E. stain.)

FIG. 30. Necropsy 9867. Renal artery. Few polymorphonuclears in intima. (H. and E. stain.)



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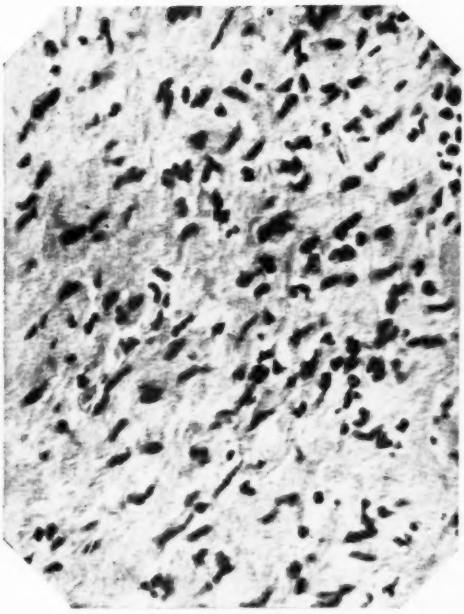

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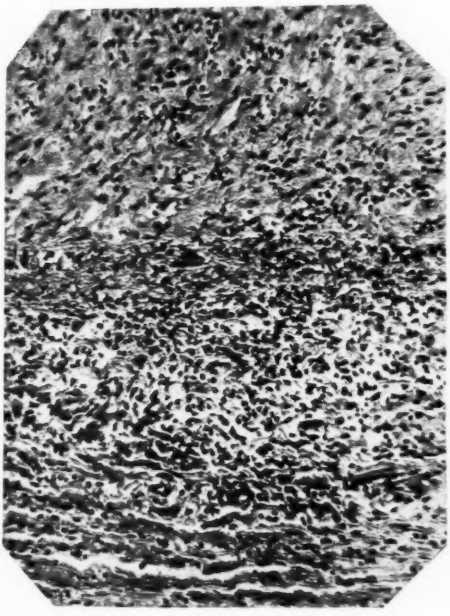

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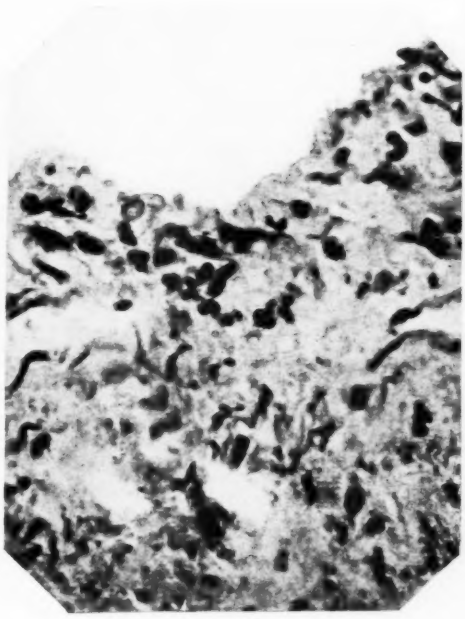


30

Pappenheimer and VonGlahn

Pathology of Rheumatic Fever

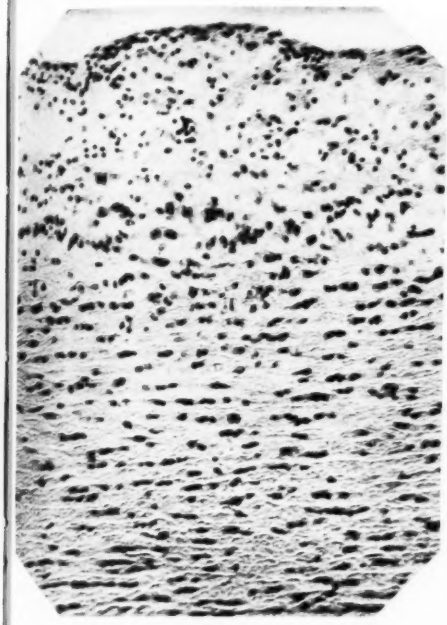
PLATE 155

FIG. 31. Necropsy 9529. Rheumatic aortitis and early atheroma. Beneath the atheromatous area are bands of non-nucleated fibrillar material surrounded by large basophilic cells. (H. and E. stain.)

FIG. 32. High power of a portion of field shown in Fig. 31. Large basophilic cells about bands of non-nucleated fibrillar material.

FIG. 33. Necropsy 9529. Rheumatic aortitis. Infiltration of intima and adjacent portion of media with large mononuclear cells and polymorphonuclears. The nuclei of many of the cells are greatly distorted. (H. and E. stain.)

FIG. 34. Same as Fig. 33, high power.



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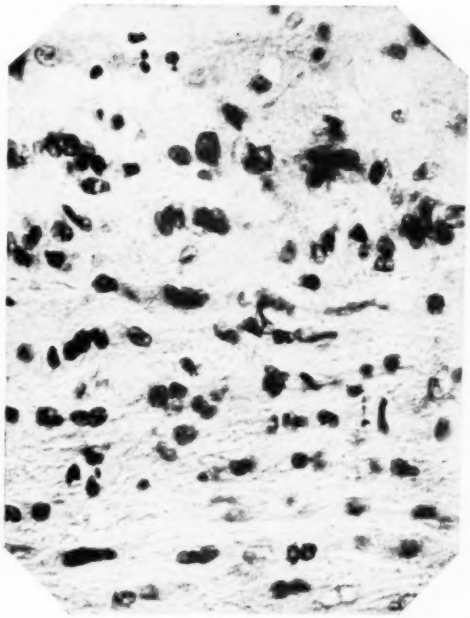

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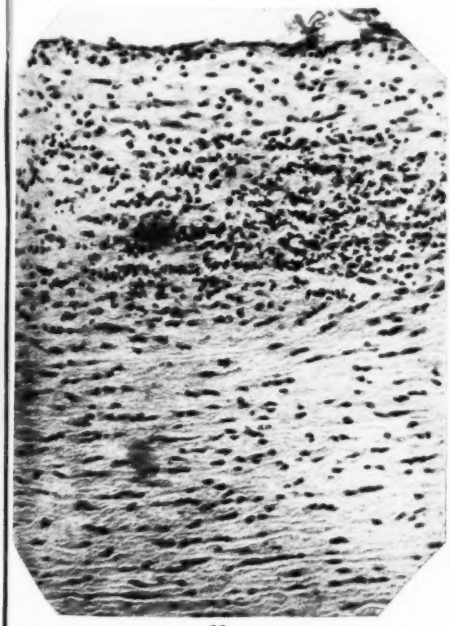

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34

Pappenheimer and VonGlahn Pathology of Rheumatic Fever

MALFORMATIONS OF THE HEART INCLUDING TWO CASES WITH COMMON ATRIOVENTRICULAR CANAL AND SEPTUM DEFECTS AND ONE WITH DEFECT OF THE ATRIAL SEPTUM (*COR TRILOCULARE BIVENTRICULOSUM*) *

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I. COMMON ATRIOVENTRICULAR CANAL AND SEPTUM DEFECTS

Although absence of the membranous part of the interventricular septum is a rather common heart anomaly, absence of the entire membranous septum combined with a common atrioventricular canal and an aperture in the lower atrial septum is quite rare. It represents a definite type of cardiac malformation, six cases of which are to be found described in the literature. In addition Keith [1] states that he has seen fourteen others and cites two described by Griffith, so that altogether we have found descriptions of, or reference to, twenty-two such cases. As the literature has not been exhaustively studied, some cases may have been overlooked, especially from European literature. However, recent discussion of the subject by Mönckeberg [2] seems to preclude this possibility.

CASE 1

Clinical Report: The patient was a girl, one year old, a Mongolian idiot, who died in the Children's Hospital (No. 1384) with symptoms of cardiac insufficiency. Clinically, signs of an enlarged heart, a systolic murmur and gallop rhythm, led to the diagnosis of a congenital heart lesion. The previous history and family history of the case are irrelevant. The Wassermann reaction was negative. The necropsy took place eight hours after death.

Anatomic Diagnoses: (1) Defect of the atrial septum, with numerous perforations of the same, and patent foramen ovale; defect of the upper part of the ventricular septum; persistence of a common atrioventricular ostium, with abnormal development of the atrioventricular valves.

* Received for publication June 24, 1927.

(2) Extensive hypertrophy and marked dilatation of the heart, especially of the right side, with fatty degeneration of the myocardium. (Weight 50 gm. in fixed condition; circumference at base, 14 cm.; transverse diameter, 4.6 cm.; base to apex, 6.5 cm.)

(3) Chronic passive congestion of the lungs, liver, and spleen.

(4) Partial fetal atelectasis of both lungs.

(5) Mongolian facies.

(6) Aplasia of the third phalanx of the left fifth finger.

Description of the Heart

The heart is large and generally dilated; its apex is rounded. The dilatation is more marked on the right side, especially in the atrium and auricular appendix. The left auricular appendix is unusually small and appears rudimentary.

When the heart is opened there appears a gross defect of the upper part of the interventricular septum and of the lower part of the interatrial septum, as well as an undivided atrioventricular canal, all four chambers thus communicating freely. The interventricular septum is totally defective in its membranous portion, presenting instead, in this region, an aperture of communication between the ventricles. The muscular septum, the upper margin of which is bow-shaped with its convexity downward, forms the lower boundary of the interventricular aperture. The anterior margin of the aperture curves sharply upward to the right semilunar aortic cusp. Anterior to the aperture the ventricular septum is normal and forms the posterior wall of the conus. The inferior margin of the aperture slopes in a gentle curve upward and backward to the posterior wall of the left atrium. From this region there extends into the aperture a finger-like process which will be described later. The extent of the aperture represents that area which is normally occupied by the small membranous interventricular septum, the membranous atrioventricular septum and the junctional region of the atrial and ventricular septa. The aperture measures 3 cm. in an anteroposterior direction, and 1.4 cm. from the line of attachment of the atrioventricular valves to the free margin of the septum.

Both sides of the septum show abundant trabeculae, many of which are exceedingly fine. If the spaces between the trabeculae are carefully probed with a fine, blunt instrument, at least half a

dozen points of communication between the two ventricles may be found in different parts of the septum.

The common atrioventricular canal is surrounded by valve cusps which are better developed on the anterior than on the posterior side. They arise from the aorta and from the fibrous junction between atria and ventricles and are attached below to papillary muscles and to the anterior and inferior boundaries of the interventricular aperture.

The anterior papillary muscle in the left ventricle is well developed and the posterior is absent. In the right ventricle all three papillary muscles, the large anterior, the anterior medial and the posterior medial, are well developed. The large anterior papillary muscle lies somewhat closer to the septum and has a rather more extensive attachment to it than is usual. The anterior medial papillary muscle, which consists of four or five groups of chordae, springs from the upper, anterior portion of the interventricular septum, or, dorsal wall of the conus, just anterior to the interventricular aperture. The two muscles comprising the posterior medial group do not stand away from the heart wall but resemble more closely the trabeculae carneae.

In the left ventricle a large cusp corresponding in position to the aortic cusp of the mitral valve is conspicuous. When viewed from the aortic side it is found to arise from the base of the aorta below the adjacent halves of the left and posterior semilunar cusps. It is attached to the anterior papillary muscle and to the anterior boundary of the interventricular aperture by chordae tendineae, and to the region between the right and posterior semilunar aortic cusps by a small fibrous sheet. The chordae which pass to the anterior margin of the aperture appear as if the membranous atrioventricular septum of a normal heart were shredded into chordae tendineae. The sheet of fibrous tissue which occupies the region between the right and posterior aortic cusps corresponds to the extreme upper portion of the normal, membranous, interventricular septum.

Laterally, the aortic cusp of the mitral is continuous with a small cusp which arises from the annulus fibrosus and which is attached to the anterior papillary muscle. Medially the large aortic cusp becomes continuous, by means of a strand of valve tissue, with a cusp in the right ventricle comparable in position to the anterior leaflet of the tricuspid. The strand is similar to those often seen

connecting cusps in the normal heart. It is attached to the upper part of the interventricular septum anterior to the aperture by one of the several groups of chordae which comprise the anterior medial papillary muscle.

The anterior and lateral cusps of the tricuspid are attached as follows: the anterior, to the anterior medial papillary muscle and to the large anterior muscle; the lateral, which corresponds to the posterior cusp of the normal heart, to the large anterior and the posterior medial muscles. This is presumably normal. The lateral cusp, however, is poorly developed in that portion which lies against the posterior wall of the ventricle, being closely applied to the wall like the papillary muscle to which it is attached.

Lying against, and closely applied to the posterior half of the interventricular septum in the right ventricle, there is a cusp corresponding in size and position to the posterior half of the medial leaflet of the tricuspid. It arises from the upper posterior portion of the interventricular septum, and is attached in two places. The attachment to the posterior papillary muscle consists of only one or two chordae; the attachment to the septum is by several chordae lying beneath the cusp and by two long chordae stretching obliquely forward to be attached to the anterior half of the septum.

There remains, finally, a rudimentary cusp, the finger-like process referred to above. It is a fibrous mass, measuring 7 mm. in length and about 3 mm. in diameter. It projects freely into the aperture and is continuous over the posterior margin of the ventricular septum with the medial leaflet of the tricuspid. From its under surface there arise chordae which are attached, not directly to the septum, but to a narrow membrane, 7 mm. long and 3 mm. high, which in turn is attached to the upper margin of the interventricular septum in its posterior half.

The atrial septum shows conspicuous malformations. It consists almost entirely of a sheet of fibrous tissue, corresponding to the valvula foraminis ovalis of the normal heart. It is perforated all around its periphery by numerous foramina ranging in diameter from 1 to 5 mm. The muscular portion of the atrial septum (limbus) is limited to the upper anterior region of the septum and passes downward to become continuous with the musculature of the anterior wall of the atrium. The limbus does not quite overlap the upper anterior curved margin of the valvula foraminis ovalis and

the muscular part is not fused to any extent with the fibrous septum. The atrial septum as a whole is not in the same plane as the ventricular septum. Its anterior attachment is in line with that of the ventricular septum, but its posterior line of attachment is displaced toward the right, so that the mouth of the coronary sinus which is located just to its right, lies, not above the medial cusp of the tricuspid, as in the normal heart, but above the posterior cusp. The posterior line of attachment of the atrial septum is 2 cm. to the right of that of the ventricular septum.

In the right atrium neither the valve of the coronary sinus nor the valve of the inferior vena cava is to be found. An extremely delicate fibrous cord, attached to the atrial wall just below and lateral to the mouth of the sinus, and above to the superior wall between the two venae cavae, is seen hanging free in the atrium. This may possibly represent the remains of an undeveloped right sinus valve.

Interpretation

From our knowledge of the development of the heart, there can be no doubt that the malformation described depends upon two departures from the normal developmental processes: failure of fusion of the endocardial cushions, and persistence of the interventricular foramen. However, embryologists are not entirely agreed as to certain details in the normal course of these processes, so that before attempting to explain the anomalous features of this heart on the basis of these disturbances, the subject must be discussed in some detail. What seems fairly certain is that these disturbances date back to the first two months of intra-uterine life, for according to Mall [3] the development of the septa, ending with the closure of the interventricular foramen, is complete at an embryonal length of about 16 to 18 mm.; the embryo according to Arey [4] attains a crown-rump length of 17 mm. by the end of the seventh week.

On the subject of fusion of the endocardial cushions, and obliteration of the foramen ovale I, Mall differs from Tandler [5] and from Mönckeberg in one fundamental respect. According to the last two authors the interatrial septum (primum) grows downward to meet the endocardial cushions and fuses with them; Mönckeberg particularly emphasizes the presence of the lower margin of the atrial septum and upper margin of the ventricular septum, at the level of

the atrial canal, as a prerequisite for the fusion of the endocardial cushions. They form, according to this author, a sort of bridge across which the cushions may travel toward each other. In cases of patent foramen ovale I (primary interatrial foramen) with normal valves, the ventricular septum alone performs this function. He attributes the persistence of the primitive undivided atrial canal to a primary growth failure of both septa. On the other hand, Mall, in describing the closure of foramen ovale I, assigns more extensive growth to the cushions and less to the atrial septum; indeed, according to him, the obliteration of this foramen is due to the continued growth and fusion of those parts of the cushions which project into it. In an embryo of 9 mm. he describes the fused cushions as a "cubical plug which blocks the center of the atrial canal"; he does not specifically state that the foramen ovale I in this embryo is patent, but at 11 mm. he states: "The complete union of the two cushions has obliterated the foramen ovale I." Whether fusion of cushions in the atrial canal antedates obliteration of the foramen, or is coincident with it, is not specifically stated, but certainly, according to Mall, the fusion of the cushions with the atrial septum, as well as obliteration of foramen ovale I, is due to growth on the part of the cushions, and the original atrial septum never extends down to the level of the atrial canal.

It seems to be generally accepted that the definitive atrial septum is formed of three elements, the septum primum, septum secundum and the lower portion of the left sinus valve (Tandler). After septum I is well developed and perforated to form foramen ovale II, septum II appears as a feeble elevation at the right of septum I, extending downward from the postero-superior wall of the atrium. Septum II, continuing to increase in height, extends forward along the superior wall of the atrium and then downward along its anterior wall, and finally backward to meet the forward projecting left valve of the sinus venosus. The union of these two forms the limbus. Mall, who does not describe the formation of the atrial septum, does not mention the septum secundum. To Mall, all the elevations participating in the division of the primitive atrium, atrial canal, and bulbus are but parts of the subendocardial tissue which he describes in considerable histologic detail; they are not sharply separated from each other. Thus he describes at 7, 8, and 9 mm., both before and at the time of the fusion of the endocardial

cushions, prolongations of the cushions which extend upward "to the sinus venosus and are blended with the connective tissue above it." Again at 11 mm. he describes the fused mass (endocardial cushions) as extending up to the "atrial septum on its dorsal side and to the left valve of the opening into the sinus venosus." It is impossible to avoid the conclusion that the prolongations into the right atrium from this mass of connective tissue represent at least the lower part of Tandler's septum secundum. The attempt to apply Tandler's terms to these prolongations is made because it seems to establish an early continuity between the endocardial cushions, especially the posterior, on the one hand, and the septum secundum and sinus valves, especially the left, on the other. This connection is of interest in the anomalous heart under consideration.

In this heart the muscular portion of the atrial septum is defective. The lower limb of the limbus is absent. We may conclude that that portion of septum II which should have grown downward and curved backward, and there fused with the left valve of the sinus venosus, failed to develop in the usual manner. Furthermore, since the derivatives of the right sinus valve are also absent, a failure of development of both sinus valves seems to be indicated. It is possible, of course, that the valves of the coronary sinus and inferior vena cava were obliterated by the great dilatation of the right atrium, but more probably they were poorly developed, and hence left no trace in the atrium unless the fibrous cord mentioned above represents the right valve. If, as we have attempted to show, septum II of Tandler is either formed entirely, or increases in size, by the addition of those prolongations of Mall into the right atrium, then, failure of development of septum II and at least retarded development of the sinus valves, particularly the left, would in turn be dependent upon underdevelopment of the cushions, particularly the posterior. That in this heart the posterior cushion was deficient, will be shown later.

Another factor, however, may have contributed to the failure of fusion of the left valve of the sinus venosus with the endocardial cushions; namely, the obliquity of the atrial septum. Since the mouth of the coronary sinus lies so far to the right of the ventricular septum, this distance may have prevented the valve from fusing with the prolongation from the cushions.

Septum I apparently attained its usual growth, for it forms the

fibrous interatrial septum of the heart, separating the atria throughout at least three-quarters of their extent. Moreover, the upper free margin of the valvula foraminis ovalis is seen from the left side in its usual location at the upper anterior portion of the atrial septum. If, as Mall believes, the closure of foramen ovale I is due to the growth of the anterior and posterior cushions, the persistent interatrial aperture must be due to deficient growth of these cushions. The only features pointing to defective development of septum I, are the numerous small foramina perforating the fibrous septum. These might well be due to the fact that septum I was not reinforced all around its margin in the usual manner by septum II.

The obliquity of the atrial septum and the abnormal position of the coronary sinus, seem to be due to too great displacement of the opening of the sinus venosus. Early in embryonic development the opening of the sinus into the common atrium is made smaller by a fold coming in from the left side, and separating sinus from atrium (Tandler). In this way the sinus comes to open into the right side of the atrium. Septum I then develops just to the left of the mouth of the sinus. In this heart, the mouth of the sinus seems to have been pushed farther to the right than usual. The displacement of septum I may in turn have been partially responsible for the inability of the cushions to extend into and close foramen ovale I.

Regarding the interventricular septum, embryologists generally agree that coincident with the fusion of the atrial septum and cushions, the muscular interventricular septum increases in height and the bulbar septum grows down to meet it. During and after the fusion of these two septa, the interventricular foramen is reduced in size by continuous down-growth of the cushions. On the details of the above process, however, as well as in terminology, the various authors differ materially; they especially disagree on the exact mode of final closure of the interventricular foramen. It would lead us too far to go into the details of the controversy in which are included the opinions of Tandler, Mönckeberg, Sato, Born and Mall. Essentially the opinions held by these authors represent views varying more or less widely from the original description of His. It appears, however, that the diminution in size of the interventricular foramen is attributed to upward growth of the ventricular septum or down-growths from the cushions; its final closure to the bulbar septum, the cushions, or both.

In the heart under consideration, the complete separation of the pulmonary artery and the aorta and the well developed upper anterior part of the ventricular septum speak for the normal development of the entire septum aortopulmonale. The numerous intertrabecular apertures discernible on probing may be regarded as evidence that the ventricular septum was somewhat underdeveloped. Mönckeberg regards these as remnants of the spongy trabeculae composing the septum. The large aperture is, however, not much larger than a normal membranous septum would be, and it seems quite probable that it was somewhat increased in size during dilatation of the heart. We conclude, therefore, that the ventricular septum was not greatly deficient in its growth.

Certain structures found in the place of the membranous septum and apparently derived from the anterior and posterior cushions, seem to indicate the part played by the cushions in the formation of the septum. For example, the chordae and fibrous leaf which attach the finger-like mass of endocardial tissue to the posterior margin of the aperture, may represent that process from the posterior cushion which, according to Mall, normally grows downward along the posterior margin of the foramen. Inasmuch as the chordae attaching the anterior cusp of the mitral valve to the anterior margin of the septum occupy the same position as the membranous septum of a normal heart, it would seem that they represent cushion material which normally goes into the formation of the membranous septum. In a recent report of a heart similar to this, Schleussing [6] describes a small fibrous area lying "in the normal location of the pars membranacea" (between right and posterior semilunar aortic cusps?) and believes that this part of the septum membranaceum is formed by the bulbar septum. In our heart a similar small fibrous sheet is found, but it attaches the aortic cusp to the base of the right semilunar cusp, and is clearly similar to the chordae tendineae lying immediately below it. Our heart seems, therefore, to offer some evidence in favor of the theory advanced by Sato [7] that the cushions are entirely responsible for the closure of the interventricular foramen.

Regarding the development of the atrioventricular valves, the original description of His seems, on the whole, to stand unchallenged. As to the exact part played by the endocardial cushions, both medial and lateral, in valve formation, His, Sato, and Mall

seem to be the only authors who have fully discussed this subject. Mall, who agrees with His, shows by the study of a graded series of human embryos that the medial cusp of the tricuspid is derived from the right ends of both cushions, and that the anterior medial papillary muscle is formed by the fusion of the septum aortopulmonale with the medial end of the right lateral cushion. It, therefore, marks the boundary between the anterior and right lateral cushions, and may be used in the interpretation of anomalous valve formation. Sato's theory of valve formation has usually been the accepted one, namely, that the right end of the anterior cushion takes part in the formation of the anterior cusp of the tricuspid.

It should be stated, in favor of the Mall theory, that Mall actually finds at one stage of development, the medial cusp of the tricuspid and the aortic cusp of the mitral hanging like curtains over the septum; this points toward the derivation of the medial cusp, like the aortic, from both endocardial cushions, and not as Sato believes, from the right end of the posterior only. Mall finds, also, in numerous embryos of less than 20 mm., that the two venous ostia are quite alike; each is bordered by a medial and lateral cusp, and each ventricle has a papillary muscle or set of muscles between the medial and lateral cusps. Finally, Mönckeberg describes in a trilocular heart, with single atrium but completely formed ventricular septum and atrioventricular cusps, the two medial cusps (aortic of the mitral, and medial of the tricuspid) continuous with each other over the top of the septum.

In this heart, the aortic cusp of the mitral is obviously derived from the left end of the anterior cushion, and is, therefore, the equivalent of that half of the normal aortic cusp which lies farthest from the septum. The small strand of tissue connecting the aortic cusp with the anterior of the tricuspid is, in the light of Mall's theory, derived from the right end of the anterior cushion; like the anterior end of the normal medial cusp, it is attached to the anterior medial papillary muscle of the right ventricle. The right end of the anterior cushion may have been more deficient in its growth potentialities than the left end. It may, however, have remained small secondarily, for all the cusps lacked the stimulus for development which would have been supplied had the cushions fused. Mall describes an attachment between the septum aortopulmonale and the right end of the anterior endocardial cushion similar to that be-

tween the septum and lateral cushion. The only attachment acquired by the right end of the anterior cushion (to the septum aortopulmonale) tended, therefore, to draw it to the left, rather than out into the right ventricle and further hindered its increase in size.

As to the posterior cushion, the small medial cusp of the tricuspid was formed from its right end, and is, therefore, from Mall's standpoint, the equivalent of only the posterior half of the normal medial cusp. The posterior cushion failed to send a prolongation down into the left ventricle; consequently there is no cusp to correspond to the septal half of the aortic; in turn, no posterior papillary muscle was developed in the left ventricle. The posterior cushion material which should have gone into the aortic cusp is represented by the finger-like process. Marked underdevelopment of the posterior cushion is indicated by the character of its derivatives.

The right lateral cushion and the heart wall posterior to this cushion gave rise to the anterior and lateral (posterior) cusps of the tricuspid. The left lateral cushion gave rise to the small lateral cusp found in the left ventricle, which is the only representative in this heart of the normal posterior cusp of the mitral. The remainder of the posterior cusp, which should have been derived from the heart wall posterior to the lateral cushion by a process of undermining, was probably hindered in its development by the absence of the posterior papillary muscle.

The above interpretation of the anomalous valves, based on Mall's description of the embryologic development of the heart, seems to us most acceptable. Another interpretation, based on the theory of Sato, is, however, possible. According to his theory, the anterior cusp of the tricuspid is normally formed from the right end of the anterior cushion plus the major part of the right lateral cushion. In the light of this, the small strand of valve tissue which connects the aortic cusp of the mitral with the anterior of the tricuspid, represents, not the right end of the anterior cushion, but only that part of the cushion which lay above the interventricular septum. If this theory is correct, the anterior cushion was quite normal and the failure of fusion of the two cushions would have to be attributed almost entirely to growth failure of the posterior cushion.

Summary

The essential features of the heart described are as follows:

1. A large aperture of communication between the two sides of the heart, involving the lower atrial and the upper ventricular septa.

2. A fibrous interatrial septum, the posterior attachment of which, together with the coronary sinus, is displaced to the right.

3. A common atrioventricular canal bordered by five cusps — in the left ventricle, a small lateral and a large anterior, and in the right, a large anterior and small lateral and medial. The lateral corresponds to the posterior of the normal tricuspid valve.

4. A mass of endocardial tissue attached to the posterior margin of the interventricular septum, and projecting into the interventricular aperture.

It is obvious that the defects in this heart are the result of failure of fusion and imperfect development of the endocardial cushions, incomplete formation of septum II, and displacement of the mouth of the sinus venosus to the right. If Mall's description of the mode of closure of the foramen ovale I is accepted, the persistence of this foramen must be due to primary growth deficiency on the part of the cushions, rather than of septum I, as is commonly held. If the views of Mall regarding the relations of the lower portions of the left sinus valve are reconciled with those of Tandler, as we have attempted to do, it appears that imperfect formation of septum II may also be due to growth deficiency of the cushions. We have shown how the abnormal valves of this heart could be interpreted either in terms of Mall's or of Sato's descriptions of valve formation. Finally, since much of the site of the normal membranous interventricular septum is occupied by chordae tendineae, this heart seems to offer some evidence that the cushions normally play an important part in, if indeed they are not entirely responsible for, the closure of the interventricular foramen.

Case 2

Clinical Report: The patient was a female child, aged four months, who died in the Children's Hospital (No. 2776). Physical examination showed Mongolian facies, malnutrition, cyanosis, a loud murmur over the precordium, and a short fifth digit. The Wassermann reaction was positive. The necropsy took place three and one-half hours after death.

Anatomic Diagnoses: (1) Defect of the atrial septum, with patent foramen ovale; defect of the upper part of the ventricular septum; common atrioventricular canal with abnormal atrioventricular valves. Patent ductus arteriosus.

(2) General hypertrophy and moderate dilatation of the heart especially of the right auricle. (Measurements in the fixed condition: apex to base, 4.3 cm.; transverse diameter, 3.8 cm.; circumference at base, 11.0 cm. Weight: 33 gm.)

(3) Mongolian facies.

(4) Purulent bronchitis and lobular pneumonia.

Description of the Heart

The muscular interventricular septum, which in its thickest portion measures 0.9 cm., has a concave upper margin which forms the lower boundary of the interventricular aperture. The aperture measures 1.5 cm. in an anteroposterior direction, and 0.7 cm. from the line of attachment of the atrioventricular valves to the free margin of the septum.

The upper anterior portion of the septum differs somewhat from that of the preceding heart. A muscular process from the anterior part of the septum extends backward and upward under the right aortic cusp to the posterior cusp. In the normal heart, as well as in the preceding, the area just under the point of junction of the right and posterior cusps is fibrous, forming in the normal heart, the uppermost part of the membranous septum; in this heart, this region is muscular.

Probing between the trabeculae of the ventricular septum reveals a number of points of communication between the ventricles.

The valve cusps surrounding the common atrioventricular canal are five in number — two anterior, which are continuous with each other through the aperture; a single posterior, common to both ventricles; and one lateral in each ventricle.

The papillary muscles of the left ventricle are normal, namely, an anterior and a posterior. In the right ventricle the posterior medial muscle may be considered normal. The anterior medial is represented, as in many normal hearts, by a group of chordae attached to the crista supraventricularis, or posterior wall of the conus; of this group, only one is fleshy. The anterior (large anterior) papil-

lary muscle is rather small. The moderator band, extending from the vase of the anterior papillary muscle to the ventricular septum, is unusually large in this heart, being thicker than the anterior papillary muscle itself, and short enough to hold the anterior and septal walls of the right ventricle in close apposition.

In the left ventricle there is a large cusp corresponding to the lateral half or two-thirds of the aortic cusp of the mitral. It arises from the lower margin of the adjacent halves of the left and posterior aortic cusps. Its lateral margin is attached to the anterior papillary muscle of the left ventricle. The upper part of its medial margin is attached by chordae tendineae to the anterior portion of the upper curved margin of the ventricular septum and to that muscular process which extends backward under the right aortic cusp. This attachment is made by chordae, which are not, however, completely separated from each other but are united into a sheet by a delicate web of endocardium stretching between them. From the lower part of the medial margin of the aortic cusp, chordae pass across the top of the septum to attach to the right surface of the septum.

The cusp just described is continuous by means of a narrow strand of valve tissue with the anterior cusp in the right ventricle. This strand is attached by chordae to the free margin of the septum in its upper anterior portion, and to the crista by means of some of the chordae (including the only fleshy member of the group) which we have called collectively, the anterior medial papillary muscle. The remainder of the chordae comprising this group attach the medial border of the anterior cusp of the right side to the crista supraventricularis; the lateral border of the same cusp is attached to the anterior papillary muscle. This cusp arises from the annulus fibrosus lateral to the conus. The lateral cusp in the right ventricle, which corresponds to the posterior of the normal heart, is attached by chordae both to the anterior and to the posterior medial papillary muscles.

The posterior cusp is well developed, in fact rather redundant, and is common to both ventricles, extending across the septum. In the right ventricle it is attached to the posterior medial papillary muscle, to the right surface of the septum and to the posterior part of the upper margin of the septum. Of those chordae which are attached to the septum some extend well forward to obtain attach-

ment to a rather prominent muscular projection from the moderator band. In the left ventricle the posterior cusp is attached to the left posterior papillary muscle. The lateral cusp in the left ventricle is narrow, and is attached to both anterior and posterior papillary muscles.

The atrial septum of this heart is somewhat better developed than that of the preceding. Though the disposition of the muscular portion is similar, ending below on the anterior wall of the right atrium, it comprises rather more of the atrial septum than in the preceding case. The fibrous portion (valvula foraminis ovalis) is thicker and not perforated. As in the preceding heart, its lower free margin forms the upper boundary of the interatrial aperture. The upper curved margin of the fibrous portion of the septum, falls just short of being overlapped by the muscular portion, thus forming a patent foramen ovale II. This septum is nearly in the same plane as the ventricular septum, its posterior attachment being displaced only very slightly to the left, instead of markedly to the right, as in the preceding case. Neither the valve of the coronary sinus nor of the inferior vena cava is present. As in Case I, there is a great discrepancy in size between the two atria and auricles (auricular appendices), the right being very much larger than the left. This difference is especially marked in the auricles.

Interpretation

Since the heart in this case is in all essential features similar to the one previously described, the interpretation given for that heart will apply to this one. However, there are a few points of difference which must be discussed. The shifting of the mouth of the sinus venosus to the right, which in the preceding case, was assumed to explain the obliquity of the atrial septum, apparently does not occur in this heart, for the mouth of the coronary sinus lies directly above the right side of the ventricular septum. The derivatives of the posterior endocardial cushions are not so conspicuously underdeveloped as in the preceding. Both cushions are deficient, however, as compared to the normal.

The well developed muscle connecting the septal and anterior walls of the heart, which we have called the moderator band, presents difficulties. Mönckeberg believes that the septum aorticum

(*i. e.*, probably that portion called swelling A by Tandler), as it grows down to meet the ventricular septum, divides into two limbs, one passing to the left, and the other to the right of the ventricular septum. The limb which passes to the right, carries the right branch of the atrioventricular bundle downward, and forms the moderator band. As was noted, the posterior cusp in this heart, obviously derived from the posterior cushion, is attached by chordae to a small papillary projection on the moderator band. For an explanation of this, three possibilities suggest themselves: (1) That Mönckeberg's theory of formation of the moderator band is incorrect; (2) that the muscle in question, in spite of its location, is not actually the moderator band; (3) that the posterior cushion, growing down into the right ventricle, obtained an accidental attachment to the moderator band. The latter possibility is not inconsistent with Mall's description of the formation of papillary muscles and chordae tendineae; nor do the chordae in question extend farther forward on the septum than chordae attaching the posterior half of the medial cusp of the tricuspid to the septum in many normal hearts.

Brief Review of Similar Cases from Literature

Preisz [8] describes two cases, both in new-born children. In neither was the membranous atrial septum (valvula foraminis ovalis) as well developed as in these hearts; in both, the atrial canal was surrounded by four valve cusps, a large anterior and posterior, and two small laterals. In one case the anterior cusp was attached to the anterior limb of the interventricular septum; in the other, this attachment was absent.

Hart [9] reports two cases, one aged two years, and the other ten months. Both showed large anterior and posterior atrioventricular valve cusps, whose chordae attached in the right ventricle. One of the cases, however, showed complete absence of the atrial septum. It is, therefore, a trilocular heart with ventricular septum defect, and does not strictly belong in the same class as the hearts under discussion. It has not been included in the total.

Mönckeberg describes one case in a child of nine months. The atrial septum was fibrous and perforated to form a foramen ovale II; its lower margin reached to a distance of 1 cm. from the atrioventricular canal; the septum secundum was entirely absent. The

common atrial canal was guarded by large anterior and posterior cusps (lateral cusps are not mentioned); and under the posterior aortic cusp was located a mass of endocardial tissue about the size of a grape seed. The midportion of the crest of the ventricular septum, forming the lower margin of the aperture, was free from valve tissue, as in our cases.

Schleussing [6] reports two cases, one in a female Mongolian idiot of nine and one-half months, and another in a new-born child. The first, in which the atrial septum was similar to the first of our hearts, was complicated by some degree of transposition of the great vessels, and by the fact that the medial limb of the bulbar septum passed to the right of the ventricular septum. The valve cusps were five in number, a large anterior, continuous across the ventricular septum, two laterals and two posteriors. In the second case the atrial septum showed a large foramen ovale overlaid anteriorly and above on the right side by a perforated membranous fold. The cusps were four in number, a large anterior and posterior, and two laterals. He found in both cases a structure which he interpreted as the pars membranacea.

Keith [1] states that he has seen fourteen cases, all remarkably alike. He does not consider that the atrial septum was defective, though his figure shows a condition like that of the hearts described here. Unless the atria show a much larger aperture than in these cases he does not regard it as a persistent foramen ovale I. He states that failure of fusion of the endocardial cushions is always associated with some other grave defect, such as transposition of the great vessels or stenosis of the pulmonary artery; but in only two cases other than Keith's have defects of the great vessels been reported. In one of Preisz's cases the pulmonary valve had only two cusps; in one of Schleussing's cases there was partial transposition and narrowing of the aorta.

Keith also cites two cases similar to his, described by Griffith.

II. Common Atrium, Completely Divided Ventricles, and Imperfectly Formed Tricuspid Valve

This type of heart, with completely separated ventricles and common atrium, is called by Mönckeberg, *cor triloculare biventriculosum.*

Case 3

Clinical Report: The heart is that of a male child, who died at the age of two months, in the Children's Hospital (No. 1971). The child was one of twins, born prematurely at the end of the seventh month of pregnancy. The only findings at necropsy, other than the abnormal heart, are general atrophy of the organs, hemorrhages in the pleura, lungs and capsules of the kidneys, and a marked slant of the palpebral fissures characteristic of Mongolism.

Description of the Heart

The heart is approximately normal in size and presents no abnormalities externally. When it is opened, the two atria are observed to be in wide communication. The atrial septum is represented only by a low muscular fold which extends from the left side of the coronary sinus to the lower margin of the defect just mentioned. The muscular fold extends forward for about two millimeters along the top of the membranous septum, forming the posterior part of the lower boundary of the aperture. The anterior part of the boundary is formed by the line of fusion of the membranous septum with the aortic cusp of the mitral valve.

The ventricular septum is completely formed. Its membranous portion is considerably larger than usual. The latter lies below the interatrial defect, and has a triangular process extending backward below the rudimentary atrial septum. On the right side, the membranous septum is not covered by the tricuspid valve as in the normal heart, because of malformation of this valve; a few small nodular thickenings appear on this surface. The top of the membranous septum is continuous with the medial third of the aortic cusp of the mitral, the two merging into each other without interruption.

Both cusps of the mitral and the papillary muscles of the left ventricle may be considered normal. The cusps of the tricuspid present certain malformations. Both they and the papillary muscles in the right ventricle are smaller than normal. With the exception of the posterior, the cusps are nodular and adherent to the septum or wall of the heart against which they lie. The posterior cusp is

quite free; it arises from the posterior and lateral portions of the atrioventricular junction, and sends numerous fine chordae tendineae to the posterior medial papillary muscle and to the adjacent portion of the septum. The medial cusp is deficient in its anterior one-third; it arises from the upper margin of the muscular portion of the interventricular septum. It is adherent to the septum and might be described as a patch of nodular and thickened endocardium on that portion of the septum. Its lower margin, however, is free, and from this margin chordae pass to the posterior medial papillary muscle and to the septum. It has also a single chorda passing to the lowest point of junction of the membranous septum with the muscular septum.

Between the membranous septum and the crista supraventricularis there is a crumpled mass of valve tissue from which two groups of chordae pass, one to the surface of the membranous septum itself and to the lowest point of junction of membranous with muscular septum, and the other to the lowest point of the crista. The latter group of chordae are gathered together and are attached to a single, fairly well developed papillary muscle which constitutes the major portion of the anterior medial muscle.

The crumpled mass just described is directly continuous with the anterior cusp of the tricuspid. This cusp is fairly smooth, but, like the medial, is closely adherent to the heart wall, excepting that portion which joins it to the crumpled mass. From this junctional piece, a single chorda passes across the crista and is attached within the conus to its posterior wall. This chorda and the single papillary muscle mentioned above, comprise the anterior medial papillary muscle. The chordae of the anterior cusp pass to the large anterior papillary muscle. The latter is poorly developed, consists of two trabeculae, and lies against the lateral (anterior, in the normal position of the heart) wall of the ventricle.

Interpretation

That septum I was deficient or entirely absent in this heart seems clear. Because of its location medial to the mouth of the coronary sinus, the rudimentary atrial septum, which is muscular, seems to have been derived from the left valve of the sinus venosus. It corresponds to the lower and posterior part of the normal limbus of the fossa ovalis. Its continuity with the posterior part of the mem-

branous septum recalls the early fusion between an upward prolongation of the posterior cushion in the right atrium, and the left valve of the sinus venosus (Mall).

The cusps in the right ventricle will be interpreted first in the light of Mall's theory of valve formation. As noted previously, the anterior medial papillary muscle marks the boundary between the anterior and right lateral cushions. Examination of a series of normal hearts, has shown that both medial and anterior cusps are usually attached to the muscle and that it may consist of several parts, either muscular or tendinous. In the heart under discussion, it consists of a group of chordae attached to a fairly well developed papillary muscle, and a single chorda passing into the conus. The point between these two is taken as approximately the line of demarcation between the anterior and lateral cushions. The crumpled mass, therefore, represents the right end of the anterior cushion. Since this mass is distinctly separated from the medial cusp of the tricuspid, the latter, in this heart, seems to have been derived from the right end of the posterior cushion alone. The right ends of the cushions apparently failed to fuse.

Another interpretation, based upon the theory of valve formation as given by Sato, is possible. Sato holds that the normal medial cusp of the tricuspid is derived from the right end of the posterior cushion alone, and that the right end of the anterior cushion goes into the anterior cusp. The crumpled mass, if regarded as part of the medial cusp, must be a part of the posterior cushion, split off secondarily; if regarded as belonging to the anterior cusp, it is the right end of the anterior cushion. In the latter case, it must be assumed that the growth potentialities of the posterior cushion were insufficient to form a normal medial cusp.

In a recent study of malformations of the heart, Mönckeberg has no cases exactly similar to this one. He describes, however, one case of *cor triloculare biventriculosum*, in which there was no vestige of the atrial septum, and in which the apex was cleft.

Summary

The heart just described presents, in addition to almost complete absence of the atrial septum, defects of the tricuspid valve, especially its medial cusp. The defect of the atrial septum is due to absence

or degeneration of the septum primum, and to absence of the septum secundum. The rudimentary atrial septum is interpreted as the left valve of the sinus venosus. The defective medial cusp of the tricuspid is interpreted as due either to failure of fusion of the right ends of the endocardial cushions (if Mall's description is accepted), or to deficient growth potentialities of the posterior cushions alone (according to the theory of Sato).

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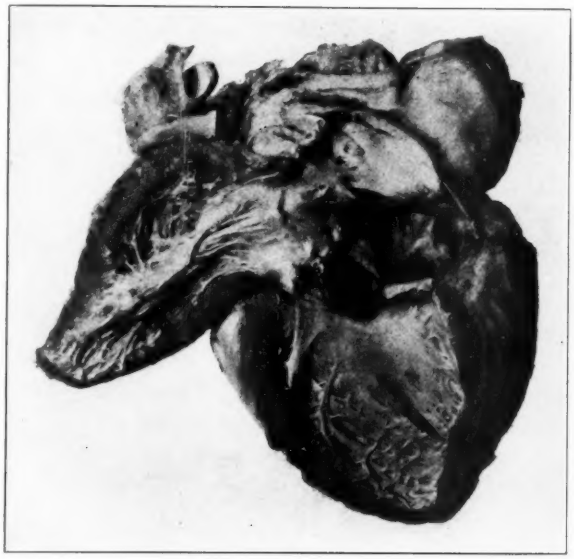
DESCRIPTION OF PLATES

PLATE 156

FIG. 1. Left atrium and ventricle of heart from Case 1. The finger-like process projecting into the aperture from the posterior heart wall is seen to the right of the aperture.

FIG. 2. Right atrium and ventricle of heart from Case 1. The finger-like process is here seen projecting into the aperture from the left.



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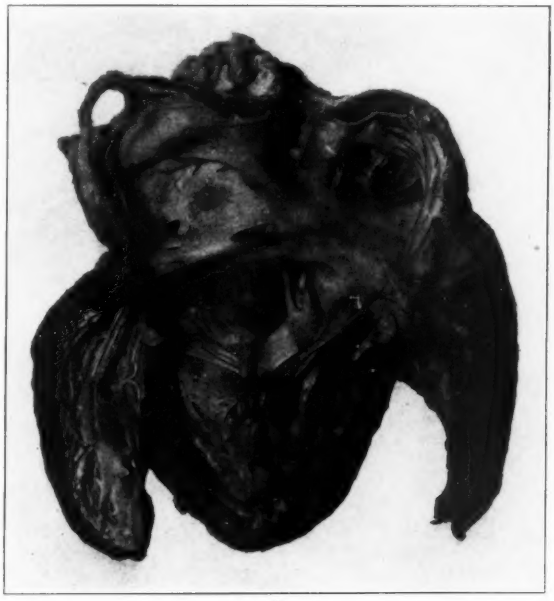

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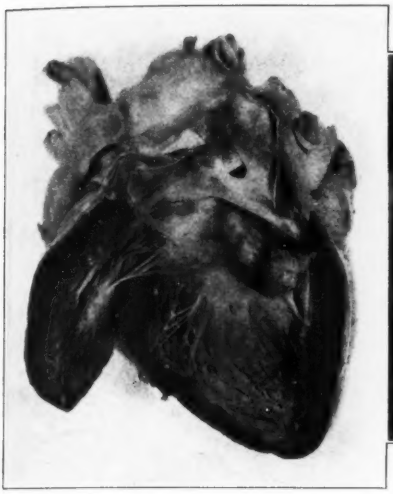
Plate 157

Fig. 3. Region just below the aorta from the heart of Case 1. The attachment to the base of the right semilunar cusp is by a small sheet of fibrous tissue, and to the anterior margin of the aperture by chordae tendineae.

Fig. 4. Left atrium and ventricle of heart from Case 2.

Fig. 5. Right atrium and ventricle of heart from Case 2.

Fig. 6. Region just below the aorta from the heart of Case 2. The attachment to the muscular process that extends backward under the right semilunar cusp as well as to the upper part of the anterior margin of the aperture is by chordae tendineae, which are joined together by a delicate web of endocardial tissue. The lower chordae pass through the aperture to the right side of the top of the septum.



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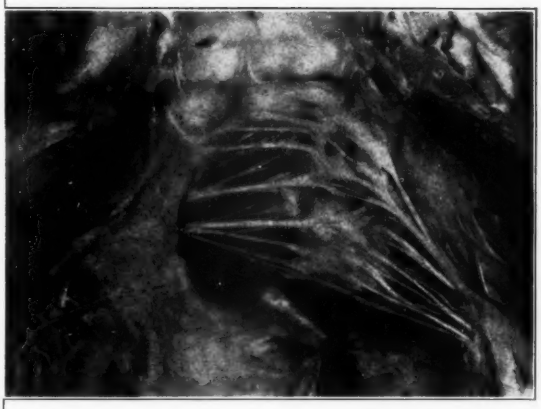

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Gunn and Dieckmann Malformations of Heart

Plate 158

Fig. 7. Right atrium and ventricle of heart from Case 3, the anterior wall of the heart removed.

7

A CONGENITAL ANOMALY OF THE HEART: TRUNCUS ARTERIOSUS COMMUNIS*

H. M. Zimmerman, M.D.

(From the Department of Pathology, Brady Memorial Laboratory, Yale University School of Medicine, New Haven, Conn.)

In view of the infrequent occurrence of the congenital anomaly of the heart, truncus arteriosus communis, it seems desirable to report a case of this kind which occurred during the past year on the Pathology service of the New Haven Hospital. Moreover, several unusual features make this case particularly interesting; namely, the age of the patient, the unusual blood supply to the lungs and the apparent lack of previous cardiac symptoms. No complete review of the literature is attempted, for Dr. Abbott has done this in a recent article [1] in which a summary of the literature and other sources of study reveal but twenty-three cases of this anomaly. The case history given below is that of the oldest patient presenting a truncus arteriosus communis to come to necropsy. Vierordt reported one dying at sixteen and another at nineteen years of age. Crisp's patient lived to twelve years. The other patients in this series died in early childhood or infancy.

The embryologic factors responsible for cardiac malformations are discussed in detail by Abbott and Shanly,[2] and, therefore, will not be repeated here. The arteries supplying the lungs in this case, one to each lobe, appear to be derivatives of the branchial arches of the fetus.

Report of Case

History: A fairly well developed and well nourished black male, aged 25 years, was brought to the New Haven Hospital in an unconscious condition as the result of an automobile accident. On admission the patient had a contusion and laceration over the left eye. The pulse was 68 per minute and the blood pressure 140 systolic and 74 diastolic. A regular irregularity of the heart, ap-

* Received for publication July 5, 1927.

parently of long standing, was noted. A "machinery" murmur was heard over the sternum. Respirations were slow and labored. The pupils were active and equal, and there was bleeding into the posterior pharynx. The patient did not regain consciousness and died four hours after admission. A history of previous cardiac symptoms was not obtained.

Necropsy: The examination was performed eleven hours after death. Only the findings bearing on the subject are here included. The body is fairly well developed and nourished and weighs 47.7 kilograms. The finger nails have a decided double curvature, but there is no clubbing of the phalanges. As the chest plate is removed it is noted that the heart's transverse diameter is unusually great and that the diameter from base to apex is relatively short. No pulmonary artery is seen *in situ*, and so the heart and lungs, together with the aorta as far as the bifurcation of the common iliac arteries are removed *en masse*.

The heart is large and very firm, and is estimated to weigh over 500 gm. The apex is broad and not very well defined. The epicardium is smooth and glistening but for a gray elevated plaque 3 cm. in diameter on the anterior surface near the base. A moderate amount of subepicardial fat is present along the course of the coronary arteries. The auricular appendages nearly surround the common truncus arteriosus (Fig. I, T. A.), which arises from the left side of the base of the heart. No evidence whatever is present of a pulmonary artery or of a ductus arteriosus. The ascending portion of the truncus is wide, and a short distance beyond its junction with the transverse portion gives rise to the right innominate, left common carotid and left subclavian arteries in the normal manner. Just beyond this latter vessel the truncus narrowed perceptibly, and here, from the right lower surface of the arch of the truncus, arises a vessel (Fig. I, 1) which courses beneath the arch toward the left and enters the upper lobe of the left lung. At its origin from the truncus this vessel measures 6 mm. in diameter. One and one-half centimeters beyond this, from the right side of the truncus, another vessel (Fig. I, 2) arises, measuring 8 mm. in diameter at its origin. This vessel passes transversely in front of the trachea, just above the bifurcation, to enter the upper lobe of the right lung. This vessel bifurcates just before it enters the lung. One centimeter beyond this

vessel, and arising from the same side of the truncus, a small artery (Fig. II, 3) 2 mm. in diameter, passes transversely behind the lower portion of the trachea to enter the middle lobe of the right lung. Here also, from the under surface of the arch of the truncus, arises an artery (Fig. II, 4) 4 mm. in diameter passing obliquely downward to supply the lower lobe of the right lung. One centimeter beyond this last vessel, and from the left side of the beginning of the descending portion of the truncus, arises an artery (Fig. II, 5) 12 mm. in diameter, which passes horizontally toward the left to enter the lower lobe of the left lung. Just before it enters the lung this vessel also bifurcates. At this level the truncus, which follows the normal course of the thoracic and abdominal aortae and gives rise to the arteries usually derived from these vessels, measures 4.5 cm. in circumference.

The cavity of the right atrium is approximately three times the size of the left. The foramen ovale is closed. The valves of the inferior vena cava and coronary sinus are well formed. Two left pulmonary veins open by a short common trunk into the very small left auricle and two similar veins from the right lung also unite a short distance from the lung to enter this auricle.

The left ventricular wall measures 15 mm. in thickness, and the right wall at a corresponding level measures 12 mm. The interventricular septum averages 20 mm. in thickness. The capacity of the left ventricle is at least three times that of the right. The endocardium of all four chambers is everywhere smooth and glistening. The papillary muscles of both ventricles are greatly hypertrophied and the columnae carneae stand out as thick cords from the ventricular walls. The tricuspid valve is delicate and velamentous and the chordae tendineae insert well beyond the free edge of the valve. Two chordae arise from the muscular interventricular septum below and in front of the septal defect and insert into adjacent parts of the anterior and median cusps of this valve. This interventricular defect measures 1.5 cm. in diameter and readily permits the insertion of one finger. It is situated between the upper border of the ventricular septum and the lower surface of the semilunar valves of the common truncus. Its anterior, posterior and lower limits are formed by the anterior and posterior walls and the muscular septum respectively. Above, it is bounded by a valve-like structure which

is the remains of the pars membranacea. This membranous structure is inserted above between the anterior and the right posterior cusps of the common truncus. Below it is attached to the medial cusp of the tricuspid valve by a structure resembling a chorda tendinea. Its vertical position serves to partially narrow the interventricular defect. This ventricle lacks a well marked conus arteriosus, the space between the anterior heart wall, the anterior cusp of the tricuspid valve and the right side of the remains of the pars membranacea being quite shallow.

The large truncus arteriosus arises chiefly from the left ventricle, only about one-fourth of the lumen over-riding the interventricular defect. The semilunar cusps guarding the orifice of the truncus are three in number and very large, and the sinuses of Valsalva are all very deep, readily allowing the insertion of the end of the thumb. This valve measures 8 cm. in circumference. The sinus of Valsalva behind the anterior cusp is deeply funnel-shaped. The right and left coronaries arise rather high up in the anterior and in the left posterior sinuses, respectively. No evidence whatever of the septum aortopulmonale is present, and a slight puckering of the wall of the truncus 4 cm. above the truncal valve is the only evidence of a probable ductus Botalli. The base of the truncus has a few irregularly shaped yellow arteriosclerotic subintimal plaques.

The mitral valve is delicate and velamentous and the chordae tendineae insert well beyond the free edge. From the above description of the heart, it is seen that the venous blood of the right ventricle mixed with the arterial blood of the left ventricle at each ventricular systole, for the only pathway of escape for the blood in the right ventricle is through the interventricular defect into the common truncus, which received simultaneously the blood from the left ventricle.

The following anatomic diagnoses are made after a complete necropsy:

Primary: Contusions and lacerations of the face and body; extradural hemorrhage (following rupture of middle meningeal artery).

Subsidiary: Common truncus arteriosus persistens and interventricular septal defect; apical pulmonary scar; pleural and peritoneal adhesions.

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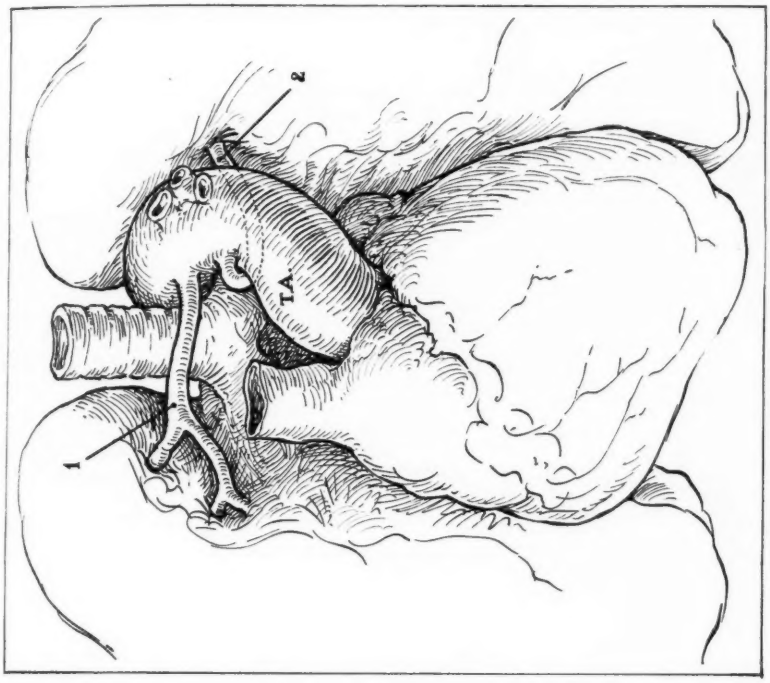
DESCRIPTION OF PLATES

PLATE 159

FIG. 1. Anterior view of heart showing common truncus and origin of pulmonary arteries to upper lobes of lungs.

FIG. 2. Posterior view of heart showing common truncus and origin of pulmonary arteries to lower lobes of lungs.



A. 1190 ANTERIOR VIEW OF HEART SHOWING COMMON TRUNCUS AND ORIGIN OF PULMONARY ARTERIES TO UPPER LOBES OF LUNGS. ☐
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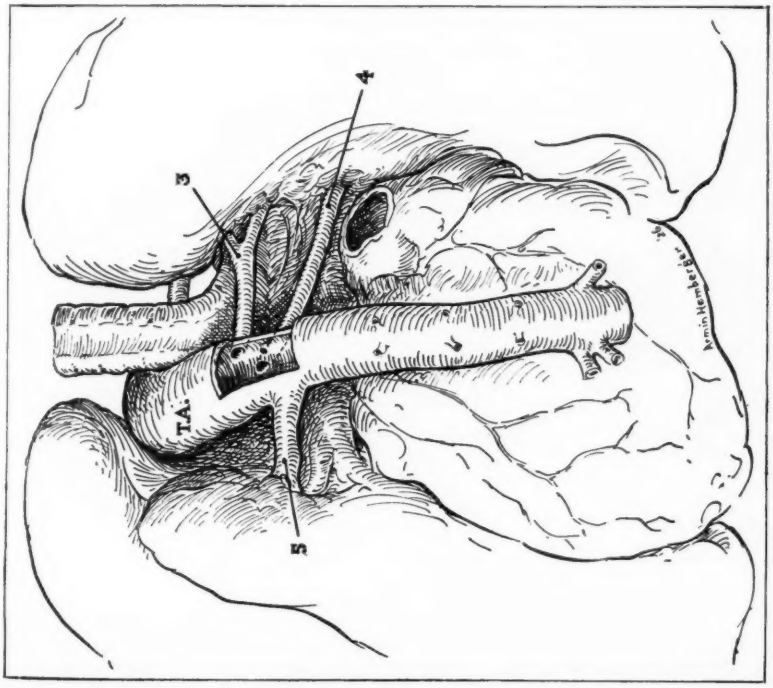
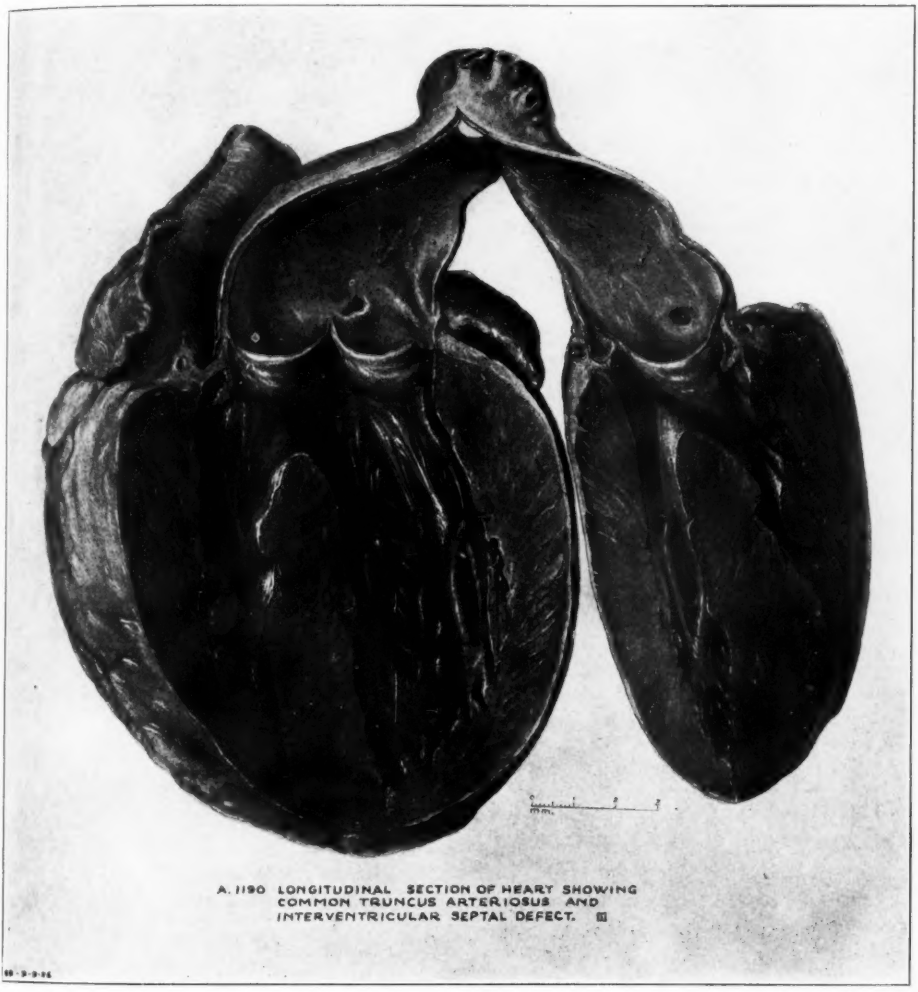


A 1190 POSTERIOR VIEW OF HEART SHOWING COMMON TRUNCUS AND ORIGIN OF PULMONARY ARTERIES TO LOWER LOBES OF LUNGS
2

PLATE 160

FIG. 3. Longitudinal section of heart showing common truncus arteriosus and interventricular septal defect.



A. 1190 LONGITUDINAL SECTION OF HEART SHOWING COMMON TRUNCUS ARTERIOSUS AND INTERVENTRICULAR SEPTAL DEFECT.

VEGETATIVE ENDOCARDITIS DUE TO THE MENINGOCOCCUS *

WITH A CASE REPORT

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Cases of vegetative and ulcerative endocarditis due to the meningococcus are unusual enough to justify placing them on record. In a fairly careful survey of the literature, reports of only eleven cases were found. In some of these cases the accuracy of the diagnosis is questionable because the details of the bacteriologic examinations are not given.

The first case was reported by Warfield and Walker [9] in 1903. The patient entered the hospital after two weeks of headache, cough, chills and delirium. There was a loud systolic murmur at the apex. At no time were signs of meningitis observed. A pure culture of meningococcus was obtained from the blood. At necropsy, acute ulcerative endocarditis of the mitral valve, mitral stenosis, and infarction of the spleen and kidneys were found. Meningococci in pure culture were obtained from the vegetation.

Weichselbaum and Ghon [8] in 1905 reported a case of typical epidemic cerebrospinal meningitis in a child 9 years of age who died in the fifth week of the disease. The necropsy showed meningitis, pericarditis and vegetative endocarditis of the mitral valve. Meningococci were cultured from the vegetation.

Westenhoeffer [7] in 1906 reported two cases of endocarditis associated with meningitis. The first, a child 1 year old, exhibited a typical example of epidemic cerebrospinal meningitis with death at the end of a month. At necropsy, meningitis and vegetative endocarditis of the mitral valve were found.

The second case was that of a woman 21 years of age who died after a five-day illness during which signs of meningitis were observed. The necropsy again showed meningitis and vegetative mitral endocarditis.

Cecil and Soper [1, 6] in 1911 made very careful observations on a case at the Presbyterian Hospital. The patient, a man 31 years of

* Received for publication August 18, 1927.

age, entered the hospital after two weeks of headache, vomiting and joint pain. The joints of the ankles and fingers were swollen and tender. Systolic and presystolic murmurs were present at the apex. The condition of the patient grew steadily worse and he died in coma at the end of a month. There was no evidence of meningitis. Meningococci grew in pure culture from the blood. The necropsy showed an adhesive pericarditis, and a thickened mitral valve with a soft, cauliflower vegetation on the anterior leaflet. Some thickening of the aortic valve and infarcts of the spleen and kidney were found. Smears and sections of the vegetation showed Gram-negative intracellular diplococci. The bacteriologic examination in this case was extremely thorough. The organism corresponded to the meningococcus in morphology and cultural characteristics. It was pathogenic for animals, fixed complement and was agglutinated by antimeningococcus serum.

In 1912 Finley and Rhea [2] recorded a case in a man, 47 years of age, who entered the hospital after three weeks of joint and precordial pain, chills and cough. There was a soft, systolic murmur at the apex, an enlarged liver, a hemorrhagic eruption of the skin and a painful and swollen finger. Meningococci were grown from the blood and spinal fluid. At the necropsy a narrow row of irregular gray-yellow, friable vegetations were found on the mitral and aortic valves. There were infarcts of the spleen and kidneys. Meningococci were obtained on culture of both vegetations and infarcts.

Mackarell [4] in 1915 recorded two cases. The first patient showed a systolic murmur at the apex, and meningococci in blood culture. Death ensued after an illness lasting twelve weeks. The second patient was ill for sixteen weeks with meningeal signs; and a pure growth of meningococcus was obtained from the spinal fluid. The mitral valve in both of these cases at necropsy showed large, granular, friable vegetations in which meningococci were demonstrated.

Fairley and Stewart [3] (quoted by Worster-Drought and Kennedy [5]) in 1916 also reported two cases. One showed fresh granular vegetations of good size on sclerosed mitral and aortic valves. The second case had fresh vegetations on two cusps of the aortic valve. In both of these cases cultures of the vegetations showed a pure growth of meningococcus.

Worster-Drought and Kennedy [5] in 1919 recorded a case of endocarditis in a man, 37 years of age, who had a definite history of

rheumatic fever. There were signs of sepsis without evidence of meningitis and he died after an illness lasting five weeks. The heart was enlarged and both systolic and diastolic murmurs were heard over the aortic area. Meningococci were grown from the blood. At necropsy a perforation of the basal portion of one aortic cusp was found which left the free edge unaffected. Projecting from the ulcerated area was a massive, tough, fibrinous vegetation, which contained meningococci.

The following is a summary of a case seen in this hospital:

Report of Case: Patient, H. L., a male negro laborer, 21 years of age, entered the Boston City Hospital Jan. 23, 1927, complaining of chills and dyspnea. The family and the past history are negative.

Present Illness: Two weeks before coming to the hospital the patient noticed marked dyspnea and palpitation, with a slight cough. There were several severe chills and the patient felt feverish up to the time of admission. He also suffered several attacks of very intense precordial pain radiating down both arms.

Physical Examination: The patient was a well nourished man, rational and quiet, exhibiting moderate dyspnea and marked cyanosis. The heart was slightly enlarged to the left. A blowing diastolic murmur was heard over the aortic area. At the apex a short presystolic and a loud blowing systolic murmur transmitted to the axilla were present. A fine thrill was felt at the apex. The rate was 140 a minute, the rhythm regular, and the sounds of fair quality. The pulse was Corrigan in character. Pistol-shot sounds were heard in the cubital fossae, groins and popliteal spaces. A capillary pulse was noted. The lungs showed dullness and rales at both bases. There were no signs of meningitis. The temperature was 101 ° F and the respirations 34 a minute. The blood pressure was 140 systolic and zero diastolic. The leucocyte count was 15,000. The urine showed a large trace of albumen with many red and white blood cells and brown granular casts in the sediment. The clinical diagnosis was acute endocarditis with aortic regurgitation.

Course of Disease: There was little change up to the time of death. The temperature subsided to 99 ° F and the rate of respirations increased somewhat. On the third day after admission he suddenly collapsed and died.

Necropsy Report

Necropsy: Performed Jan. 26, 1927, one hour postmortem. Enlarged axillary and enlarged and indurated inguinal nodes are felt.

The liver edge is 14 cm. below the xiphoid cartilage and 8 cm. below the costal margin in the right mid-clavicular line. There are a few slightly enlarged mesenteric lymph nodes.

The right pleural cavity contains about 300 cc., and the left 100 cc. of straw-colored fluid. A few fine fibrous adhesions in the right pleural cavity are noted.

Heart: The weight is 490 gm. It is somewhat larger than normal. The epicardium is smooth and glistening. The myocardium is firm and a dark brick-red color. There is no gross evidence of fibrosis. Projecting into the right auricle just below the fossa ovale is a soft, smooth, purple-red, friable mass, 1.5 cm. in diameter, which involves the medial cusp of the tricuspid valve. This vegetation fills a ragged perforation about 1.5 cm. in diameter which extends through the interventricular septum. On the left side of the heart it forms an irregular hole just below the medial cusp of the aortic valve and includes the base of the valve to the line of closure. The edges of the perforation are covered with brown, granular material which is easily broken off. Smears of the vegetation show a mass of fibrin, polymorphonuclear cells, and Gram-negative diplococci. The endocardium and valves are otherwise entirely negative. The coronaries are not remarkable.

Lungs: The upper portions are soft, spongy and gray. The lower portions are pink, somewhat firmer and crepitant. Multiple sections show no gross abnormality.

Spleen: The weight is 320 gm., and the size somewhat greater than normal. The surface is slightly wrinkled and dark purple in color. The cut surface is dark red with distinct gray markings. The consistence is firm and a small amount of pulp scrapes away.

Gastro-Intestinal Tract: Negative.

Pancreas: Negative.

Liver: The weight is 2360 gm., and the organ is somewhat larger than normal. The surface is smooth and reddish brown. The consistence is firm. Multiple sections reveal no gross pathology. The gall bladder and ducts are negative.

Kidneys: The combined weight is 420 gm. The left kidney contains several sharply circumscribed, gray to yellow areas which are pyramidal in shape with base toward the surface and the apex toward the pelvis. In these regions the normal kidney markings are obliterated. The surface of the kidney over these areas is somewhat raised, granular and adherent to the capsule. In the right kidney there are two similar lesions.

The *adrenals*, *bladder*, *genitalia* and *aorta* are negative.

Microscopic Report

Heart: The epicardium is thickened and infiltrated with lymphocytes. Between the muscle fibers there are many endothelial leucocytes, polymorphonuclear neutrophiles, eosinophiles and lymphocytes. There are a few areas which show necrotic bundles of collagen fibers surrounded by endothelial leucocytes, strongly suggesting Aschoff bodies. In certain areas there is fairly extensive necrosis of muscle fibers with replacement by granulation tissue.

Sections through the vegetations show a mass of fibrin thickly infiltrated with polymorphonuclear and endothelial leucocytes. There are masses of Gram-negative diplococci present both within and outside of cells. These can be seen in sections stained with Mallory's eosin-methylene blue, Giemsa's method and MacCallum's modification of Goodpasture's stain.

Lung: The alveoli contain a few erythrocytes, rare polymorphonuclear cells and a few endothelial leucocytes.

Spleen: A number of areas are present, particularly marked in the germinal centers, where endothelial leucocytes are grouped with masses of fibrin and some polymorphonuclear cells. Around these clumps of cells there is a proliferation of fibroblasts. Scattered throughout the organ are focal collections of plasma cells.

Liver: In the region of the central veins a few liver cells that show the hyaline cytoplasm of early necrosis are seen. A slight lymphocytic infiltration is present in the portal areas.

Kidney: There are areas of infarction necrosis where the normal structure is completely obliterated. At the periphery of these areas masses of erythrocytes and polymorphonuclear cells are grouped.

Adrenal: Negative.

Bacteriology

Cultivation: Smears of a vegetation grown forty-eight hours on sheep blood-beef infusion agar plates showed an even, sparse growth of smooth, rounded, pearly-gray, non-hemolytic colonies. The best growth took place on hydrocele agar. No growth could be obtained in liquid media.

Morphology: Smears from the vegetation and from cultures showed a pure growth of Gram-negative, biscuit-shaped diplococci. They varied greatly in their size and in the intensity with which

they stained with the dilute carbol fuchsin used as the counterstain in Gram's method.

Agglutination: Suspensions of twenty-four hour cultures on hydrocele agar slants were made in salt solution and kept at 56° C for one hour. Mixtures of equal parts of the bacterial suspension with graded dilutions of a standard antimeningococcus agglutinating serum with a titer of 1:400 were made. The mixture was kept twenty-four hours at a temperature of 55° C. Agglutination was complete up to a dilution of 1:100 and partial to 1:400. Controls with salt solution in place of the bacteria and antipneumococcus serum in place of the antimeningococcus serum were negative. A culture of gonococci similarly treated was not agglutinated.

Precipitins: The organisms were grown for twenty-four hours on hydrocele agar slants. Each tube was then washed down with 10 cc. of sterile distilled water and shaken well; the tubes were pooled, and phenol was added to the mixture to give a concentration of 0.5 per cent. The flask was kept at room temperature for a week and shaken daily. The material was then centrifuged at high speed for twenty minutes and the water-clear supernatant fluid was pipetted off and used as antigen. Standard agglutinating serum for the meningococcus was used as the source of the antibodies. A good precipitin ring was formed with an antigen dilution up to 1:600. Horse serum in place of the antimeningococcus serum and salt solution in place of the antigen gave no precipitation. An antigen made in the same fashion from a culture of gonococci gave no precipitation.

Complement Fixation: An antigen made in the same way as that used for the detection of precipitins was used. Inactivated antimeningococcus serum was used as amboceptor: 0.05 cc. of antigen fixed complement down to the point where 0.0025 cc. or less of antiserum was used. There was no fixation using horse serum in the place of the antimeningococcus serum.

Summary

A case of vegetative and ulcerative endocarditis due to the meningococcus is reported and the literature reviewed.

The identity of the organism is proved culturally and serologically.

Lesions of the myocardium resembling those seen in rheumatic fever were obtained.

I am indebted to Dr. F. B. Mallory and Miss Catherine G. Norton for the illustrations and to Miss Lillian M. Leavitt for technical assistance.

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DESCRIPTION OF PLATES

PLATE 161

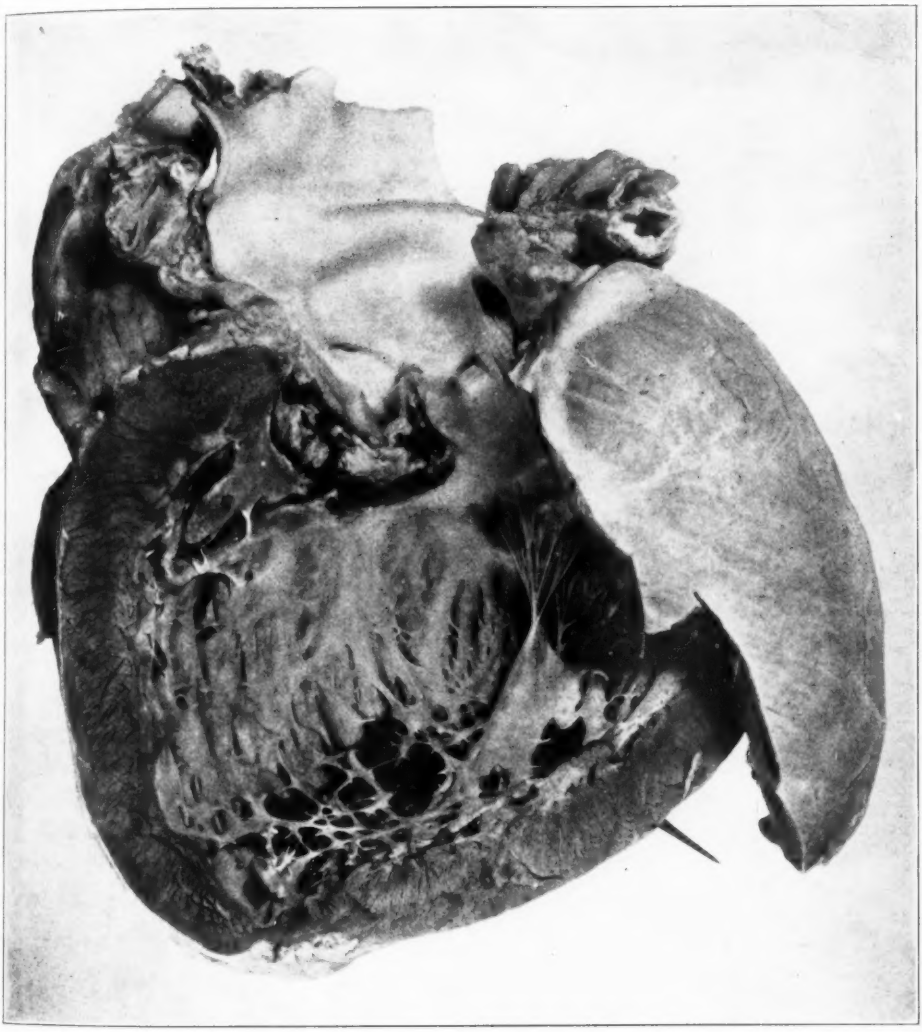
FIG. 1. Photograph of the right side of the heart showing a large, rounded vegetation projecting from the inner surface of the auricle and the tricuspid valve. Under the vegetation there has been necrosis of the interventricular septum with perforation through to the aortic valve which is shown in Fig. 2.

1

Rhoads Meningococcus Endocarditis

PLATE 162

FIG. 2. Beneath the aortic valve is a perforation of the interventricular septum and ulceration of the valve cusps with formation of vegetations.



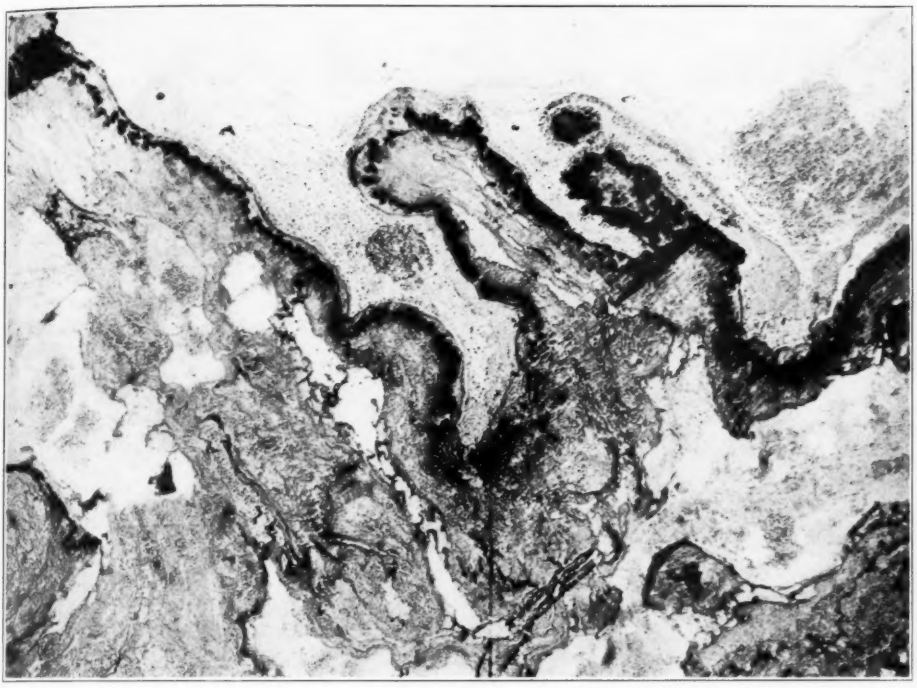
2

Rhoads Meningococcus Endocarditis

PLATE 163

FIG. 3. Photomicrograph of a section through vegetations composed chiefly of dead organisms. The dark edge is formed by masses of living cocci. × 50.

FIG. 4. Section through a small vegetation in which suppuration has taken place. × 40.



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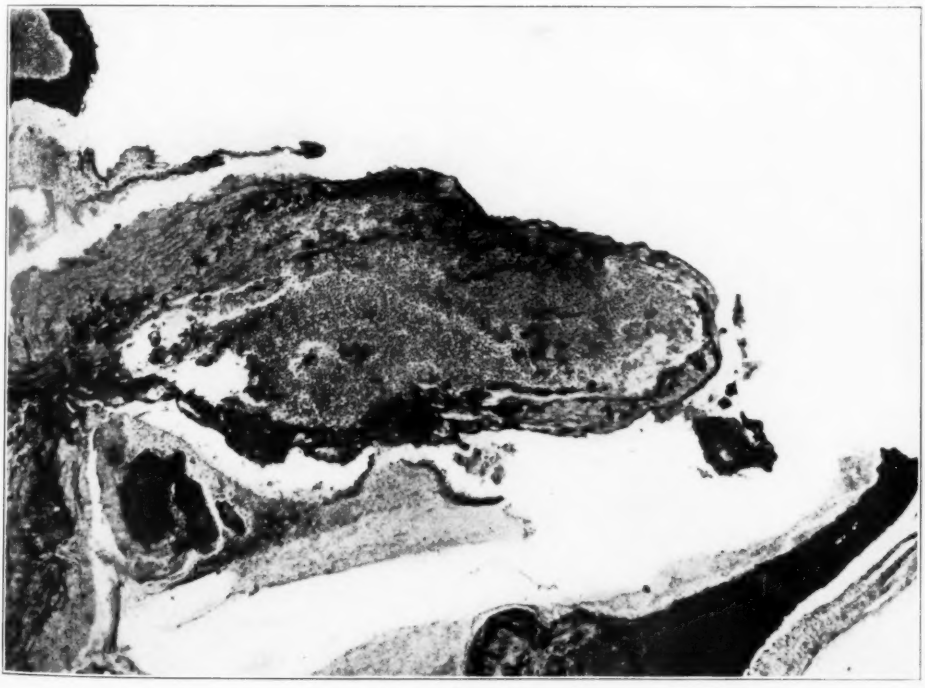


4

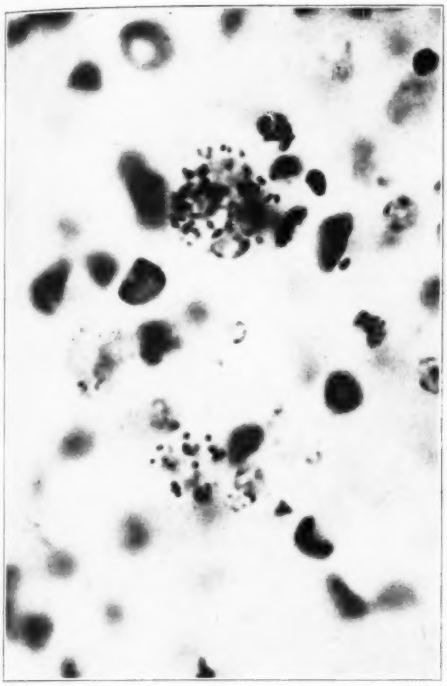
Rhoads Meningococcus Endocarditis

PLATE 164

FIG. 5. Photomicrograph showing two polymorphonuclear leucocytes containing phagocytosed Gram-negative diplococci. From an area where ulceration has allowed the escape of leucocytes from a softened vegetation. × 1500.

FIG. 6. A field in a suppurating area showing many phagocytic organisms in polymorphonuclear leucocytes. × 1500.

FIG. 7. Section through the base of a vegetation showing masses of organisms, many in phagocytic cells. × 1500.



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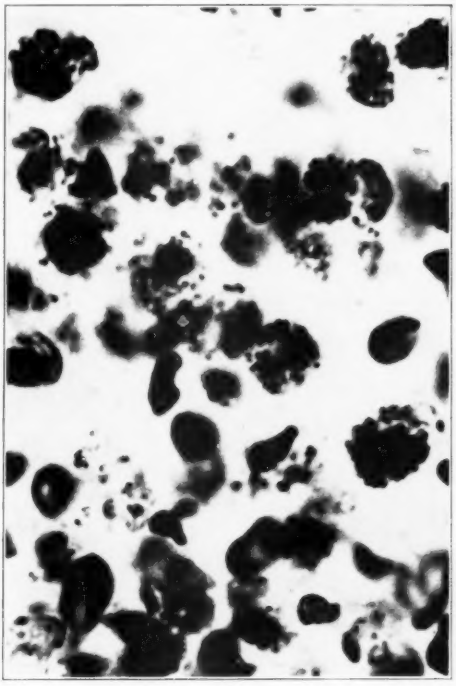

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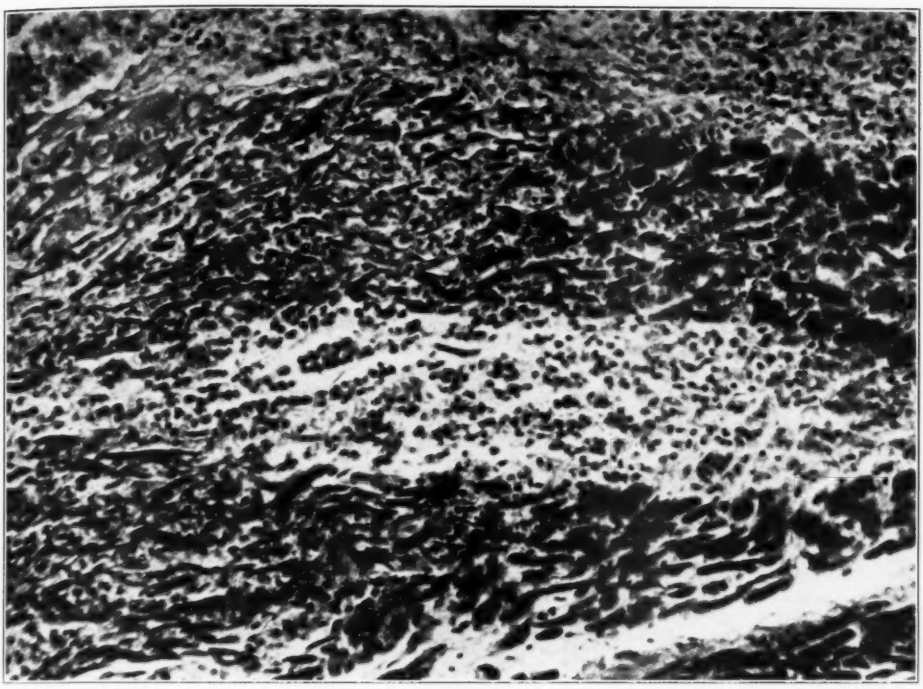
7

Rhoads Meningococcus Endocarditis

PLATE 165

FIG. 8. Section through the heart muscle near the vegetations. It shows many necrotic muscle fibers and massive infiltration with polymorphonuclear leucocytes. × 250.

FIG. 9. Section taken through the muscle of the left ventricle near the coronary artery. Endothelial leucocytes are shown grouped around a strand of necrotic collagen. This formation strongly suggests an Aschoff body. × 500.



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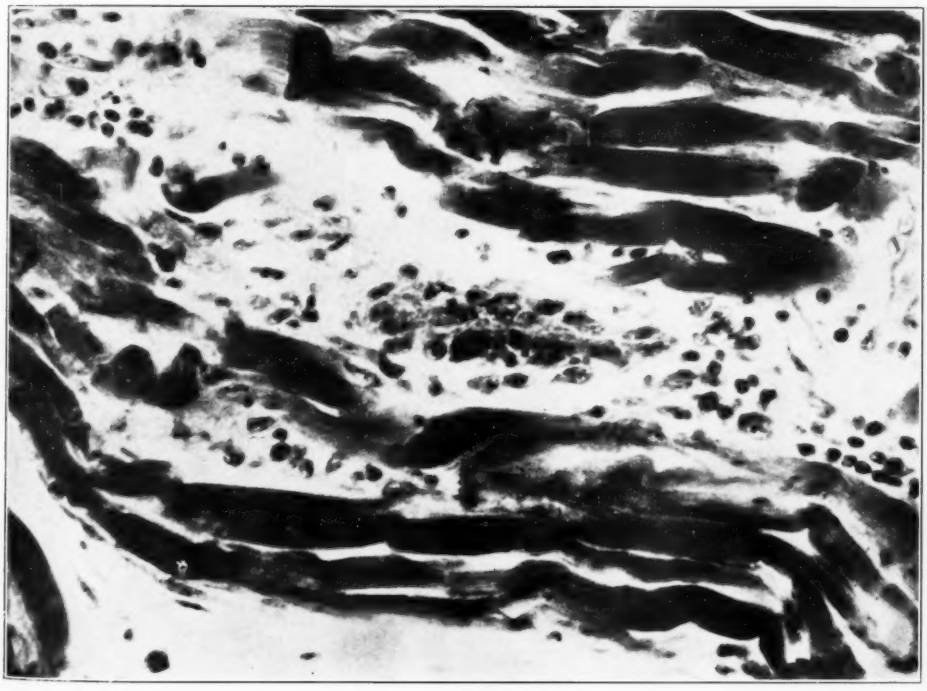

9

Rhoads Meningococcus Endocarditis

UNIV. OF MICH.

A CONTRIBUTION TO THE PATHOLOGY OF GENERALIZED ARGYRIA WITH A DISCUSSION OF THE FATE OF SILVER IN THE HUMAN BODY *

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The source of silver, found in rare instances in the human body, is therapeutic or occupational. Since the middle of the seventeenth century, when Angelus Sola advocated the therapeutic use of silver in epilepsy, tabes and chorea minor, silver nitrate has been frequently administered internally. Although keener physicians of the nineteenth century recognized the inefficiency of this treatment silver nitrate continued to be used in large doses in the conditions stated and, in addition, it was advocated in ulcerative lesions of the stomach. Lately the administration of silver nitrate internally has been abandoned. Local applications, however, still have considerable therapeutic value. In recent years various organic silver preparations have gained widespread use, especially in the treatment of certain nose and throat conditions. During such use, part of the drug is swallowed and, subsequently, through prolonged administration, a considerable amount of silver may gain entrance to the body by gastro-intestinal tract absorption. Aside from medicinal use, silver may enter the body by exposure in industrial processes when small particles accidentally penetrate the exposed skin surface of silver workers ("local disseminated argyria"). The dust of silver workshops may be the source of considerable amounts of silver in the body (Koelsch [1]). It has been assumed that the silver dust becomes absorbed both through the respiratory and the gastro-intestinal systems. Formerly one of the most common sources of industrial generalized argyria was the use of silver nitrate solution in the preparation of silver glass beads. In this process the silvering was performed by mouth suction; and by accidental swallowing of part of the solution generalized argyria resulted, which was, therefore, a common disease in Bohemia where this industry flourished.

* Received for publication August 1, 1927.

As a result of the replacement of handwork by machinery, this source of the disease became extinct (Teleky [2]).

According to whether the silver absorbed is deposited locally at the site of entrance, or carried through the entire body following entry into the blood stream and lymphatic system, argyria may be classified respectively as (*a*) local, or (*b*) generalized. The pathologic characteristics of local argyria are outside the scope of this paper. In generalized argyria the portal of entry of silver is usually the gastro-intestinal canal. Although, theoretically, silver may enter the blood stream from direct absorption through the mucous membranes, it is questionable whether the amount absorbed this way is ever sufficient to give rise to the clinical picture of generalized argyria. Argyria following the repeated local use of silver compounds in nose and throat conditions is the result of ingesting part of the silver. Menzel [3] states that following the local application of silver preparations, argyria is always caused by the portion of silver absorbed through the gastro-intestinal canal. In support of this statement he points out that generalized argyria never occurs after long continued use of silver over the conjunctiva, or following local disseminated argyria, observed in silver workers. This is explainable by the fact that in these instances sufficient silver does not enter the body because of the small size of the absorbing surface. That generalized argyria may develop as a result of direct surface absorption is shown by Olshausen's case [4] in which bluish discoloration of the buccal mucous membrane developed two months following the treatment of extensive burns with 0.1 per cent silver nitrate. In an individual reported by Crusius [5] generalized argyria developed five months after the beginning of the treatment of a burn with silver nitrate. These are the only two instances reported in which generalized argyria developed as a result of absorption of silver through the body surface. The development of argyria following intravenous administration of silver compounds is not proved. In an instance noted by Tobler [6] collargol was given by mouth and by intravenous injection. In a case discussed by Schlossberger [7] no evidence is presented that the suspected argyria resulted from the intravenous administration of silver-salvarsan.

Generalized argyria may develop also after the use of organic silver preparations, provided sufficient silver is absorbed. There are five such instances reported in the literature, Crispin,[8] Tobler,[6]

Goldstein [9] and Davis,[10] and we know of an additional unreported case in Boston. In all of these cases, silver preparations were used locally in the nasopharynx, and undoubtedly large amounts of silver entered the blood stream through gastro-intestinal absorption. As the antiseptic and astringent properties of organic silver compounds do not excel those of other chemicals, the prolonged use of organic silver preparations in the nasopharynx should be avoided.

The minimal amount of silver necessary for the production of the clinical picture of generalized argyria probably varies considerably. The determination of this amount as obtained from statements by patients gives only an approximate idea. Koelsch [1] quotes a case in which two grams of silver nitrate administered within two months produced argyria. This amount is unusually small. Krysztalowitz [11] estimated that at least twenty-five to thirty grams of silver nitrate have to be taken within a half year before the clinical picture of argyria develops. Formerly, epileptics and tabetics often received seventeen to thirty-four grams of silver nitrate without any obvious effects. A critical review of the cases reported in the literature indicates that, just as in poisoning with other heavy metals (manganese, lead, mercury), considerable variation exists between the dosage and the toxic effects produced. The predisposing factors for susceptibility and resistance are largely unknown at the present time.

The frequency of generalized argyria cannot be determined with any degree of accuracy. The cases reported in the literature do not give a correct index of the frequency of the disease. Generalized argyria was once a rather common disease. With the change in the therapeutic application of silver nitrate, and with the progress of preventive industrial medicine, however, generalized argyria became rather a disease of the past. With the recent widespread use of organic silver preparations a few new instances of the disease have been observed.

Except for the appearance of the skin, silver *per se* probably does not produce clinical symptoms and signs. Although Menzel [3] stated that some of the patients develop fatigue, restlessness and loss of appetite as a result of the withdrawal of silver following its long use, it is probable, as Koelsch [1] pointed out, that these symptoms are psychic in origin. Blum [12] observed that following the local use of argyrol in the bladder, malignant growths of the mucous membrane

occurred, and he suggested that the deposited silver may act as an irritating foreign body. It is questionable whether this suspected relation plays any rôle in generalized argyria. The reported fatal accident following the intravenous administration of collargol (Tobler [6]) cannot be attributed to silver itself (Koller-Aeby [13]). Various diseases observed in patients suffering from generalized argyria are probably accidental and it is doubtful whether silver is a predisposing factor. The first appearance of generalized argyria occurs usually over the edges of the gingiva in the form of a bluish violet margin. The location of this line is similar to that accompanying lead poisoning. There is considerable practical importance connected with this early manifestation of argyria, as the development of a "silver line" is an absolute contraindication for the continuation of the therapeutic use of silver. Following the appearance of the blue color over the gums, similar discoloration develops over the mucous membranes of the mouth, conjunctivae, sclerae and skin of the face. Gradually, then, depending on the amount of silver absorbed, the entire skin surface of the body changes color, though the exposed areas are more intensely blue than the covered surface of the skin.

The diagnosis of generalized argyria does not offer difficulties if a positive history is available, and if the change in the color of the skin is definite. Particularly if a history of taking silver is not available, early cases offer considerable difficulty in differentiating the disease from hemochromatosis and from methemoglobinemia (Firth and Harrison,[14] and Harrison [15]).

Charcot's statement that silver is eliminated by the kidneys was not confirmed by later observers. There is a possibility that traces of silver may be eliminated through the intestines.[16] All the available data agree, however, that most of the silver absorbed becomes permanently deposited in the tissues. Some caution is necessary in the interpretation of observations in man, as in the majority of instances observations as to the elimination of silver were performed after the patients ceased taking silver. It is for this reason that the question of elimination of silver during the period of intake is an open problem. Animal experiments do not throw light on the fate of silver in man, since it has not been possible to produce in animals a condition corresponding to human argyria.

Because silver once deposited becomes permanently fixed in the

tissues and because animal experimentation does not simulate human argyria, knowledge regarding the behavior of silver in man has been obtained from studies of postmortem material.

It has been possible to gather from the literature twelve cases of argyria with postmortem examinations (Fromman,[17] Riemer,[18] Liouville,[19] Neumann,[20] Weichselbaum,[21] Dittrich,[22] Jahn,[23] v. Fragstein,[24] Moslener,[25] Dohi,[26] Kino,[27] and Tobler [6]). The majority of these studies are somewhat incomplete and practically all our knowledge of pathology is based on Fromman's, Riemer's and Kino's contributions. Their investigations showed that silver becomes deposited in small, and nearly even-sized granules in the tissues. The microchemical behavior of the granules indicates that they consist of an organic silver compound, probably silver albuminate. It is stated that with the exception of brain and cord silver becomes deposited in every organ of the body. It is characteristic that silver has a special affinity for connective tissue and particularly for elastic fibers. The specific cells of organs do not contain silver, but the latter is deposited in the supporting connective tissue. The pigment deposit is most marked in the lymph nodes, in the glomeruli of the kidneys and in the choroid plexus of the ventricles. The epidermis of the skin is always free from silver. Just below the epidermis, however, and along the elastic fibers adjacent to the sweat glands, sebaceous glands and hair follicles, rich deposits of silver are usually present. In contrast to other foreign bodies, it is characteristic that silver deposits do not call out cellular reaction. According to Kino,[27] the silver granules are always extra-cellular.

In only two instances was there an attempt to determine quantitatively the amount of silver in some of the organs. Fromman [17] found 0.047 per cent of metallic silver in the dried tissue of the liver and 0.061 per cent in the dried tissue of the kidneys. Jahn [23] found 0.018 per cent silver in the fresh liver and 0.03 per cent silver in fresh kidneys.

The exact mechanism by which silver deposits are formed is not known. Fromman [17] describing his histologic studies on the first postmortem examination of argyria reported in the literature suggested that silver nitrate during its intestinal absorption changes to silver albuminate, which becomes deposited in the walls of the vessels following its loss in solubility. Riemer [18] thought that the connective tissue acts as a mechanical filter in retaining silver.

Kino [27] and others attributed a specific reducing capacity for silver to connective and especially elastic tissue. As a result of reduction the silver compound becomes precipitated.

We do not possess any therapeutic agent which may mobilize or influence the clinical picture of generalized argyria.

Because of the scarcity of careful histologic studies on generalized argyria and because the histologic and chemical observations on the case to be reported indicate that the patient was suffering from the most marked degree of argyria reported in the literature, we believe that the report of our study is of value.

Report of Case

The patient was about seventy years of age, and one of the curiosities of the Barnum and Bailey circus. For many years he was presented to the public as the famous "blue man." The patient's own story both in the circus and in the hospital was that he was suffering from congenital heart disease which suddenly became worse when he fell from a horse, while fighting as an officer in the British army in India. Although repeated attempts were made to obtain a history to show therapeutic use, or industrial contact with silver, no positive statement could be elicited. On Aug. 13, 1923 he was admitted to the Second Medical Division of the Bellevue Hospital. There was considerable difficulty in obtaining a history as he answered questions reluctantly, was suspicious and resented attention. He complained of dyspnea and orthopnea of four weeks duration and had suffered from cough for the past year. For three weeks the cough had been more intense. For some time he had suffered from nocturia three times a night. For years, walking had been difficult and unstable. His wife, who had known the patient for thirteen years, stated that during that period the color of his skin had not changed and he had only occasionally taken medication of any kind. A friend, who had known the patient for thirty years, had observed the same color since the first meeting. He gave the information that the patient had worked in silver mines. He had seen a photograph of the patient taken about thirty-five years before which showed his skin to be white.

On physical examination he was a thin old man of seventy to seventy-five years, who appeared dyspneic and orthopneic. He was in acute distress and the examination was difficult. The hair over

the scalp and the mustache were glistening white. The color of the skin was of an unusually deep blue and from a distance appeared almost black. This deep color was almost uniform throughout the entire body, although it was more intense over the exposed skin areas. The sclerae were also of a dark blue color. The pupils were contracted, small, equal and regular. They reacted sluggishly to light and the accommodation test could not be performed. Examination of the eye-grounds showed tortuous dark vessels with extensive dark bluish areas covering the eye-grounds almost completely. The patient was totally deaf on the right side and partially on the left. The mucous membranes of the mouth were similarly dark blue. The tongue was coated and dry.

The neck was normal. The respirations were labored, shallow and rapid. Anteriorly the resonance, fremitus and breath sounds were normal. Posteriorly there was dulness over both bases with numerous fine crepitant rales. The heart was slightly enlarged (11.5 cm. in 5th space). The sounds were feeble, rapid and totally irregular. The systolic murmur heard over the apex was not transmitted to the axilla. The brachial, radial, temporal and femoral arteries were tortuous and thickened. The pulses were equal, totally irregular, and there was a pulse deficit of 20. The blood pressure was 110 systolic and 80 diastolic. The temperature fluctuated between 98° and 102.8° F. The abdomen was slightly protuberant. Tenderness was observed over the epigastrium. There was pitting edema of the sacral region and over both ankles. The deep reflexes were unusually sluggish, the neurologic examination being otherwise normal. The muscles were poorly developed or perhaps atrophied. The thenar and hypothenar eminences were flattened.

The hemoglobin content of the blood was 80 per cent. The red cells were normal in appearance with no stippling. The specific gravity of the urine was 1028 with acid reaction. There was a trace of albumin with an occasional granular cast in the urine. No red cells were present. The urine did not reduce Benedict's solution.

The diagnoses of generalized argyria, generalized arteriosclerosis, myocardial degeneration, auricular fibrillation and severe circulatory failure with bronchopneumonia were made. The possibility of primary muscular atrophy was suggested.

During the following week the patient developed Cheyne-Stokes respiration. The liver edge became palpable three fingers below the

costal margin. The patient's general condition became gradually weaker and he died seven days after admission.

A postmortem examination of the body was performed Aug. 20, 1923 by Dr. Douglas Symmers with the following findings:

Necropsy Report

The body is that of a man 68 years of age, 167 cm. in length, of moderately large, well developed frame, poor musculature and nutrition. The skin of the entire body is an intense slate-blue color, with a peculiar lack of luster. The color is not modified by pressure. The skin of the head, face and neck is more intensely pigmented than that of other parts of the body. The conjunctivae present the same intense bluish gray pigmentation as the mucous membrane of the mouth. The pupils are semidilated and are even in size and outline. There are no palpable, enlarged superficial lymph nodes. The muscles of the thenar and hypothenar eminences on both sides are distinctly flattened. The interosseous spaces on the backs of both hands are noticeably deepened. The muscles of both arms and forearms and of both thighs are flabby and atrophied. The pretibial tissues are edematous, as are those of the dorsum of the foot, and pit easily on pressure. The left testicle, palpated through the scrotum, appears to be of firmer consistence than that of the opposite side.

On section, the subcutaneous fat is almost completely absent. The muscle tissues of the thoracic and abdominal walls present a dull, brownish red color. The fascial tissues, however, in these vicinities present a distinct silvery sheen. The muscles are atrophic, the individual muscle bundles separating easily.

Abdominal Cavity: The peritoneum is smooth throughout, but presents a distinct diffuse light bluish discoloration. The serosa of the intestines, both large and small, presents a diffuse slate-gray pigmentation. The diaphragm is placed normally.

Chest: On opening the thoracic cavity, no thymic remains are visible. Both pleural cavities are dry and free from adhesions. The anterior edges of the lungs meet in the midline, obscuring the upper half of the precordial area. The precordial fat is atrophic.

Heart: On opening the pericardium, there is no excess of fluid and the membrane is smooth and glistening throughout. The peri-

cardial tissues present a faint slate-bluish appearance. The heart is distinctly increased in size; the right side is markedly distended. The apex is rounded. On opening the right side of the heart, an immense quantity of thin, deep bluish red fluid blood escapes. The auriculoventricular opening on this side easily permits the entrance of three fingers. On opening the left side of the heart, a large quantity of red fluid blood escapes from the auricle. On this side the auriculoventricular opening is likewise easily permeable to three fingers. All the septa are intact. The endocardium on both sides of the heart presents a diffuse silvery blue appearance. The muscle tissue is a dirty dull brownish red, in which there is a silvery tint. The endocardium covering the papillary muscles in the left ventricle, and that of the posterior wall of the ventricle just beneath the aortic opening, is thickened and of a rather deeper bluish gray color than that of the rest of the ventricular endocardium. The valves throughout the heart show no indication of thickening. In both the aortic and mitral valves, however, are patches of silver colored pigment. The subendothelial tissues of the pulmonary artery and aorta present large, irregularly outlined, ill-defined areas which are of a silvery hue. The caliber, thickness and elasticity of the aorta and pulmonary arteries appear to be entirely normal. The heart muscle at the attachment of the posterior mitral leaflet is about 1.5 cm. in thickness. The heart as a whole is flabby and weighs 480 gm.

Lungs: The left lung is removed without difficulty. The pleura is smooth and glistening throughout. There is no excess of fluid in the pleural cavity. The left lung is fairly voluminous. Seen through the pleura, it is diffusely reddish blue in color. The pleura appears to be entirely free from pigment. On section, the organ cuts readily. The upper lobe is feathery to the touch and dry. The substance is apparently well preserved. The lower lobe, on pressure, exudes a moderate amount of frothy serum. The peribronchial lymph nodes are small and blackish in color. The right lung is essentially the same as the left.

Spleen: The spleen is normal in size and moderately diminished in consistence. On section the cut surface is smooth, bluish red, the substance abundant and the markings indistinct. No lymphoid follicles are visible. In the cut ends of the blood vessels one gains the impression that there is a certain amount of silvery discoloration.

Suprarenal Capsules: These appear unchanged.

Kidneys: The left kidney is surrounded by a moderate amount of fat. On removal, the organ appears to be slightly diminished in size. Seen through the capsule, it presents a bluish gray tinge. On section, it cuts without noteworthy resistance. The capsule strips readily and leaves behind a smooth surface in which there is a suggestion of a grayish tinge. On section, the cortex and medulla are well defined and well proportioned. The cortical markings are indistinct. Viewed by reflected light, the glomeruli stand out as sand-like bodies. In the upper pole of the kidney, on the left side, and immediately under the capsule, is a whitish, rather firm, rounded, well circumscribed mass, which measures about 1.5 cm. in diameter, one-half of which projects above the surface of the kidney; the other half replaces the substance of the organ in the immediate vicinity.

The right kidney is essentially the same as the left with the exception that it contains no nodular mass.

Liver: The liver is diminished in size. The capsule presents a diffuse bluish gray discoloration. On section, the organ cuts readily; the lobules stand out fairly distinctly as brownish red islands. The cut ends of the vessels throughout the substance of the liver are distinctly bluish gray in color. The intima of the larger veins, when laid open, is perfectly smooth but strikingly silvery in color. The gall bladder contains a quantity of dark blackish bile and some thirty or forty small, greenish brown, faceted stones. The mucous membrane of the bladder is atrophic, otherwise apparently well preserved. The larger bile ducts show no noteworthy changes.

Stomach: The serous covering of the stomach is diffusely silvery gray in color. On opening the stomach, the mucous membrane appears well preserved, except that the rugae in places have disappeared and in other places are atrophic. No focal lesions are visible.

Intestines: The serous coat of the intestines is distinctly silvery gray, but the mucous membrane appears to be well preserved.

Retroperitoneal Lymph Nodes: These are scanty in number, small in size and are apparently free from pigment.

Aorta: The abdominal and thoracic aortae present no changes other than those already mentioned.

Bladder: The urinary bladder is small and contracted. On section, the walls appear slightly thickened. The mucous membrane is thrown into a number of fine corrugations and is silver-colored throughout its entire extent.

Prostate: Except for the same silvery discoloration, the prostate appears to be well preserved.

Testicles: The right testicle on removal is found to be somewhat diminished in size. The tunica vaginalis is smooth, glistening and bluish in color. On section it cuts readily and the tubules string out easily. The cut surface is a deep mahogany color. The left testicle is decidedly smaller than normal. Its consistence is noticeably increased. On section, it cuts firmly and the cut surface presents numbers of streak-like areas which are firm to the touch and distinctly silvery in color. Approximately two-thirds of the testicular substance is thus irregularly replaced by the overgrowth of fibrous tissue.

Pancreas: The organ is long and narrow and on section presents a faintly yellowish color in which there is a distinct suggestion of grayish blue. The cut ends of the vessels, wherever seen, are distinctly bluish gray in color.

Brain: On removing the calvarium, the dura mater presents a silvery appearance. On lifting the dura, the convolutions, particularly in the frontal and parietal lobes, appear markedly diminished in size and the sulci are deepened. The vessels at the base are well preserved. On section, the substance of the brain shows no focal lesions, but both the white and gray matter have a suggestion of silvery pigmentation. The choroid plexuses are deeply pigmented, presenting a dark silvery color, almost black. The venous and osseous sinuses show no noteworthy changes, although the lining membranes of the former are silvery in color.

Anatomic Diagnoses: Generalized argyria with pronounced silvery pigmentation of the heart, including the endocardium and the pericardium; peritoneum, kidneys, liver and pancreas, particularly their blood vessels; and of the pulmonary artery and aorta; dura mater and brain, including excessive deposits in the choroid plexuses. Chronic interstitial obliterative orchitis (left side).

Chemical Examination

The results of the chemical examination warrant attention because of the extremely high silver content of the organs. The quantity of silver found in this instance is far in excess of that found in the two cases mentioned above (Fromman,[17] Jahn [23]), in which the kidneys and liver only were tested.

The Method for Isolation and Identification of the Silver

The tissue was ground, strongly acidified with nitric acid, dried, and then ashed at dull red heat. In this connection it may be pointed out that the ash may contain the silver as water soluble salts (silver nitrate, silver sulphate) and ammonia soluble salts (silver chloride, silver phosphate) and nitric acid soluble metallic silver. The ash was leached, successively, with hot water, ammonia, and 50 per cent hot nitric acid in order to get all the silver into solution. The three filtrates were combined and hydrochloric acid was added to them until all the silver was completely precipitated as AgCl. The precipitate was filtered and washed with water acidulated with nitric acid, until the filtrate was free of chlorides.

Confirmatory Tests

1. A white curdy precipitate, soluble in ammonia, in potassium cyanide and sodium thiosulphate was obtained by the above precipitation.

2. The white precipitate changed to bluish violet on exposure to light.

3. Some of the white precipitate, dissolved in ammonia, was treated with H_2S; a black precipitate resulted which was insoluble in ammonia or in HCl.

4. Some of the ammoniacal solution of the white precipitate was precipitated by H_2S; the resulting black precipitate was dissolved in hot nitric acid and evaporated to dryness. This was taken up in water and separately tested with

(*a*) Potassium iodide — yellow precipitate
(*b*) Potassium chromate — blood-red precipitate
(*c*) Sodium phosphate — yellow precipitate
(*d*) Potassium ferrocyanide — white precipitate
(*e*) Potassium ferricyanide — brownish red precipitate

The foregoing tests conclusively prove the presence of silver in the tissues.

The Quantitative Determination of the Silver

Weighed amounts of the various organs listed in the Table below were acidified with nitric acid, then dried, and ashed in an electric

furnace at a dull red heat. The ash was then leached with hot water in order to extract all soluble silver salts. It was next leached with ammonia water in order to dissolve any silver chloride and silver phosphate. Finally, it was digested with hot nitric acid to dissolve all metallic silver. The three solutions thus obtained were combined into one. The combined extracts, if not alkaline, were made so by adding ammonia. Hydrochloric acid was then added gradually, with stirring, until all of the silver was precipitated. The final solution was made slightly acid with HCl. It was then placed in a boiling water-bath for one hour and left standing in the dark for twenty-four hours. The precipitate was then filtered and washed several times with water containing a little nitric acid, then redissolved by ammonia and the solution treated with H_2S. The resulting precipitate of silver sulphide was filtered off and washed with water. It was then redissolved in concentrated nitric acid and the solution evaporated to dryness on a boiling water-bath. The residue was next dissolved in water and, if not perfectly clear, it was filtered; the filter paper was washed thoroughly and the washings added to the main solution. This solution was now acidified with nitric acid and brought to a boil. Hydrochloric acid was then added drop by drop, with stirring, until all the silver was completely precipitated. After standing in the dark for twenty-four hours the precipitate was filtered through a Gooch filter, washed with water containing a little nitric acid, until the filtrate showed the absence of any HCl, and finally washed twice with alcohol. The washed precipitate in the Gooch filter was then dried at 100° C, and finally at 130° C, until a constant weight was obtained.

The tabulated results of the quantitative analyses of the tissues follows:

Silver Content of Tissues

	Amount analyzed *grams*	Silver (Ag) recovered *milligrams*	Per cent Ag content *per cent*	Total Ag content *grams*
Kidneys	40	97.5	0.24	0.73
Heart	122	181.5	0.15	0.46
Brain	149	15.7	0.011	0.15
Liver	104	73.0	0.07	1.35
Muscles	35	54.2	0.16	45.7
Bone	62	130.0	0.21	24.4
Gall Stones	0.5	Negative	Negative	Negative

Histologic Examination

Methods: The tissue was fixed in Zenker's fluid and embedded in paraffin. The sections were stained in hematoxylin and eosin, eosin-methylene blue, phosphotungstic acid hematoxylin, Verhoeff's and Weigert's elastic tissue stains and Stewart's method for silver in tissues.

Heart: In the epicardium silver is present in small granules of uniform size and is scattered diffusely through the connective tissue. Next to the muscle where the connective tissue is loose the granules are most plentiful and they form an irregular line. They tend to be arranged in rows along the bundles of collagen fibers and follow rather closely the distribution of the elastic fibers.

The myocardium contains no silver in the muscle fibers. There are granules scattered along the collagen fibers of the intermuscular connective tissue and occasionally grouped in masses larger than a single cell. The silver tends to be most prominent where elastic fibers are most plentiful.

The arteries show a row of silver granules along the inner elastic membrane. In the muscular coat there are a few granules scattered through the connective tissue between the muscle fibers. In the adventitia there is a dense row of silver granules just outside the outer elastic membrane. The veins show rare granules except in the adventitia where a narrow row is formed. In the capillaries a thin line of granules is present in the connective tissue just under the endothelium. The vessels of the heart contain less silver than those of any other organ except the brain.

In the nerves the metal lies in scattered granules between the collagen fibers of the nerve sheath.

Lung: In the pleura, through the loose connective tissue just under the mesothelial surface, the granules of metal are distributed irregularly. As the connective tissue becomes denser near the lung parenchyma, the granules group to form a line along a heavy strand of elastic fibers, some of which appear to be beaded with silver granules contained in the fiber itself.

The alveoli show silver scattered through the connective tissue situated among collagen fibers, often close to elastic fibers. There is none of the metal in epithelium.

The arteries and veins show very few granules distributed through

the adventitia. In the alveolar capillaries the silver forms a narrow line just under the endothelium.

The bronchioles show only an occasional granule of silver in the connective tissue.

Spleen: The connective tissue of the capsule and trabeculae contains a moderate amount of silver scattered in fine particles along the bundles of collagen fibers. Along the fine fibers of the supporting reticulum of the organ the silver granules are arranged in rows, in some places marking out the fibers clearly. There are a few free phagocytic cells which contain masses of silver. Elsewhere the metal is entirely extracellular.

The vessels contain a large amount of silver. It is arranged with a few granules scattered along the internal elastic membrane and many particles quite densely packed among the elastic fibers near the adventitia. In the vessels of the spleen the metal deposit is more marked along the outer elastic membrane than in the vessels of other organs.

Pancreas: The connective tissue around the pancreas and forming the supporting structure contains isolated granules of silver irregularly distributed along the bundles of collagen with some relation to the elastic fibers.

The cells of the acini and of the islands do not contain silver. The ducts show the metal granules scattered through the fibrous tissue. The granules lie in close relation to the elastic fibers.

In the arteries the silver forms a thin line under the endothelium in connective tissue. There are a few granules between the muscle fibers and a heavy line of metal particles next to the outer elastic membrane. The veins show a fair amount of the material scattered through the adventitia.

Intestine: The epithelial cells contain no silver. Distributed through the connective tissue, between the glands, are a few granules. In the region just below the epithelium where the fibrous tissue becomes densest the particles of silver are arranged in an irregular line. The elastic fibers are not particularly numerous in this region.

Throughout the submucosa the silver granules are scattered diffusely tending to form narrow rows along the bundles of collagen, and are often in or beside elastic fibers. In the muscularis the particles follow the connective tissue as it ramifies about the muscle fibers. The capsules of sympathetic ganglia and sheaths of nerves

are marked out by narrow rows of granules. The vessels commonly show the arrangement of a few granules along the inner elastic membrane and a greater number in the adventitia near the outer elastic membrane.

Liver: In the capsule, the silver granules are scattered through the connective tissue in close association with elastic fibers. In the part of the capsule which lies next to the liver the particles are more numerous and form a rough line without apparent relation to the number of elastic fibers present.

The connective tissue about the portal areas shows a large number of silver granules scattered in close proximity to the elastic fibers. Here and there are a number of endothelial leucocytes which have engulfed one or more granules of the metal.

There is no silver in the liver cells. There are granules scattered in the strands of fibrous tissue which form the supporting structure. No metal is seen in Kupfer cells.

The arteries have a few particles in the connective tissue under the endothelium and a larger number along the external elastic membrane. In the veins nearly all the granules are in the adventitia. The ducts have a large amount of silver scattered in the surrounding connective tissue. Here there is a definite relation to the elastic fibers.

Kidney: Through the connective tissue of the capsule there are scattered granules of silver which have some tendency to follow the distribution of the elastic fibers. The tubular epithelium contains no silver. The fibrous tissue between and around the tubules contains a large number of granules. The large vessels contain very little of the metal. The walls of the glomerular capillaries contain a very marked deposit of silver. The metal is arranged in rows of granules in the delicate layer of connective tissue under the endothelium. In some places it is difficult to say that the metal is not actually in the endothelial cells. The capsular epithelium is underlaid by a narrow row of silver granules following the collagen fibers of the connective tissue.

Bladder: The epithelium contains no silver. In the submucosa there are isolated granules of metal deposited throughout. About midway between the epithelium and the muscularis the particles are massed in an irregular line. There is no relation between this line and the distribution of the elastic fibers. Through the con-

nective tissue among the muscle fibers there are silver granules along the collagen. The vessels and nerves show rare silver particles in fibrous tissue. There are a few phagocytic cells which contain granules of silver.

Aorta: A definite line of silver granules lies in the connective tissue between the intima and the media. Though there are a number of wandering cells present in the region, none is seen that contains silver. The muscular layer contains a few scattered silver granules in the connective tissue. In the adventitia the particles form an irregular line close to the media just external to the layer of elastic fibers. In the vessels of the adventitia only a few granules are present.

Brain: The choroid plexus shows a line of silver granules just under the epithelium. The particles are densely grouped in this region and it is difficult to ascertain whether or not they are in the epithelial cells. There is a small amount of silver scattered through the connective tissue. Underlying the capillary endothelium is a well defined line of granules. No silver is seen in the parenchyma of the brain. The large vessels show only a few granules in the adventitia. The capillaries are marked out by a narrow, dense line of silver particles just under the endothelium.

Skin: No silver is seen in the epithelium. In the corium there are a few irregularly scattered granules. The metal is also present in masses larger than a single cell, lying apparently quite free. Along the collagen fibers of the connective tissue adjoining the epithelium of the sweat and sebaceous glands are well defined lines of silver granules. In this region the metal is in close relation to elastic fibers.

Lymph Node: The capsule contains some scattered silver granules. Through the pulp, silver is distributed in rows of particles ranged along the supporting reticulum, in masses of clumped particles lying free in the sinuses, and is contained in phagocytic wandering cells.

To prove that the granular material present in the lymph node is silver and not carbon, concentrated nitric and hydrochloric acid was applied to the sections. This changed the color of the silver masses from dark brown or black to a light yellow, as seen under the oil immersion lens. Sections of a lung containing carbon were similarly treated without effect on the color of the pigment.

Discussion

The pathologic, histologic and chemical findings reported in this communication indicate that the patient suffered from the most severe degree of argyria ever reported in the literature. Unfortunately, the history did not indicate the amount and the form of silver taken by the patient. The clinical signs and symptoms exhibited by the patient cannot be related to argyria with certainty. The unstable gait and atrophy of the small muscles of the extremities may have some relation to the silver. Until similar additional observations are available, however, such a relation cannot be established. We wish to call special attention to the results of the chemical analysis of the tissues on account of the extremely high silver content. If we accept that the muscles represent 43.4, the bones with the ligaments 17.5, the liver 2.75, the brain 2.16, the kidneys 0.46, and the heart 0.46 per cent of the body weight (Vierordt [28]) then on the basis that the body weight of this patient was 66,400 gm. we estimate the silver content of the musculature was 45.7 gm., that of the skeleton 24.4 gm., of the liver 1.35 gm., of the kidneys 0.73 gm., of the heart 0.46 gm., and of the brain 0.15 gm. From these results a conservative estimate indicates that the silver content of the body was about 90 to 100 gm.

The histologic studies reveal that the detectable silver is present in two types of tissues: (*a*) in connective tissue, and (*b*) within phagocytic cells. In the connective tissue the silver rarely if ever is within the cell. The granules group themselves in rows along the bundles of the collagen and occasionally are in close proximity to the elastic fibers. Whether they are only along the surface, or actually within the cell cytoplasm, cannot be stated with certainty. In the fibrous tissue underlying the epithelial-lined surfaces, the silver particles are arranged where the collagen bundles are loose, without relation to elastic fibers. There is a definite tendency for the silver, as observed by other investigators, to form rows of granules in the connective tissue underlying secreting epithelium and the endothelium of vessels. In these regions there may be some relation to the presence of elastic fibers. The wandering phagocytic cells contain silver particles within the cell, an observation indicating that silver particles in the human body are not always extracellular, as stated by other observers.

The silver content of the brain was appreciably lower than that of other organs. Previous observers state that the brain and cord are the only organs not containing silver. While it is true that the silver is not deposited inside or outside of the nerve or glia cells in the brain, similarly, specific cells of other organs frequently do not contain silver. The deposit of silver in the vessels of the brain is in harmony with the general behavior of silver in the human body elsewhere. Whether the chemically detected silver corresponds to the amount of silver visible by histologic examination in the vessels, or whether beside the visible granular deposits, silver is present in other forms in the brain cannot be stated from the available data. It is of interest that on gross examination both the white and the gray matter had a suggestion of silvery pigmentation.

Summary

1. Generalized argyria may follow the absorption of both organic and inorganic silver compounds.

2. Review of the literature indicates that generalized argyria following the repeated application of organic silver preparations (argyrol, collargol) is caused by the silver ingested and absorbed from the gastro-intestinal canal.

3. The earliest appearance of generalized argyria manifests itself on the gingiva, and over the mucous membrane of the buccal cavity. Bluish discoloration over the same area is absolute contraindication for the use of silver preparation.

4. Studies on a case of generalized argyria are presented. The pathologic, histologic and chemical observations on the case indicate that the patient was suffering from the most severe degree of generalized argyria ever reported in the literature.

5. Chemical analysis of organs revealed the following concentration of metallic silver in the organs: kidneys 0.24 per cent, bone 0.21 per cent, muscles 0.16 per cent, heart 0.15 per cent, liver 0.07 per cent and brain 0.01 per cent. The total silver content of the organs was: muscles 45.7 gm., skeleton 24.4 gm., liver 1.35 gm., kidneys 0.73 gm., heart 0.46 gm., and brain 0.15 gm. The total estimated silver content of the body was 90 to 100 gm.

6. Resembling the cases reported in the literature before, there is not sufficient evidence to indicate that the silver present in the body produced any signs or symptoms except discoloration.

7. Histologic studies of the tissues indicate that the silver was present in (*a*) connective tissue, and (*b*) in phagocytic cells.

8. In the connective tissue the silver is rarely if ever within the cells. The granules have a tendency to become deposited along and between the bundles of the collagen and the elastic fibers.

9. The presence of silver granules within phagocytic cells of the spleen and lymph nodes is the only instance where the silver was observed within the cytoplasm of cells.

10. The deposited silver granules do not cause "foreign body" cellular reaction on the part of the body.

11. The affinity of silver for connective tissue and the unusually high silver content of bones suggest certain similarity between the behavior of silver, calcium and lead in the body. Among the heavy metals which may become deposited in the human body in relatively large amounts silver is of slight and perhaps least toxicity.

We are indebted to Dr. Douglas Symmers for the necropsy material obtained, to Dr. F. B. Mallory for the photomicrographs, and to Miss Lillian M. Leavitt for technical aid.

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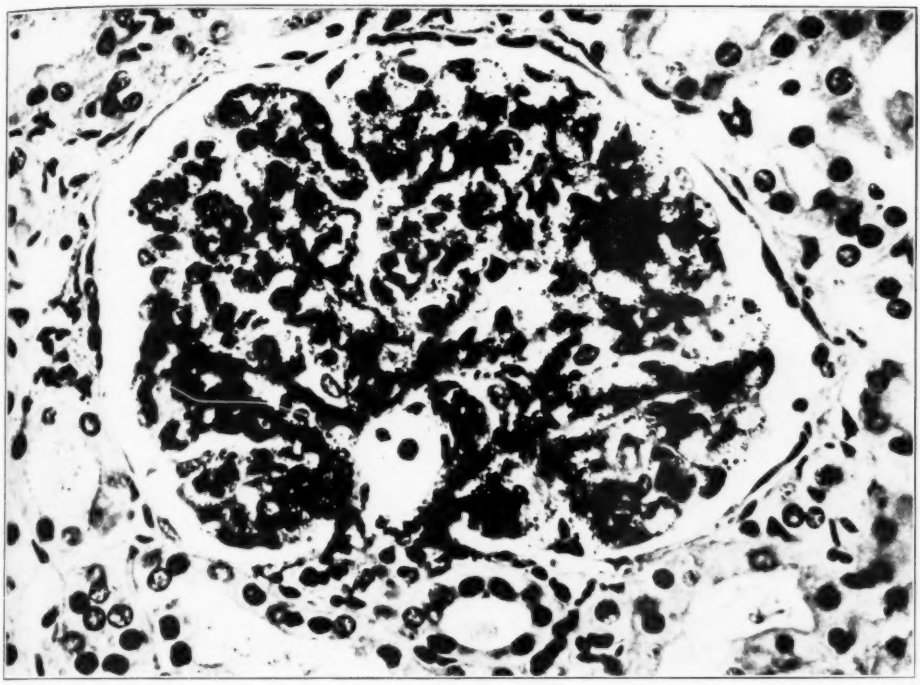
DESCRIPTION OF PLATES

PLATE 166

FIG. 1. Photomicrograph of a glomerulus showing granules of silver among the collagen fibers of the connective tissue underlying the endothelium of the capillary. × 500.

FIG. 2. Shows metal particles in the connective tissue under the epithelium of the renal collecting tubules in a pyramid. × 500.



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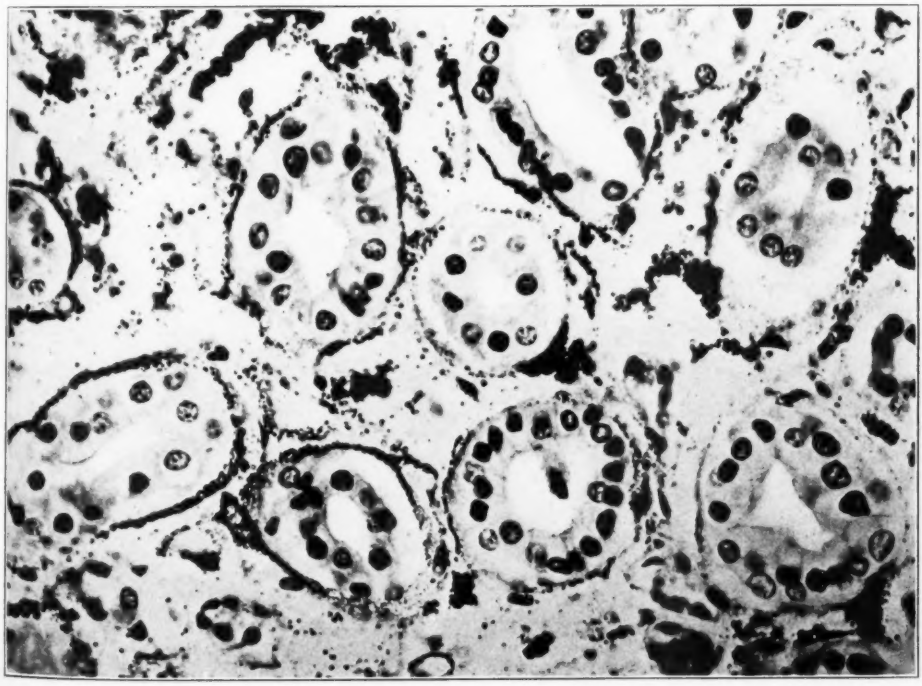


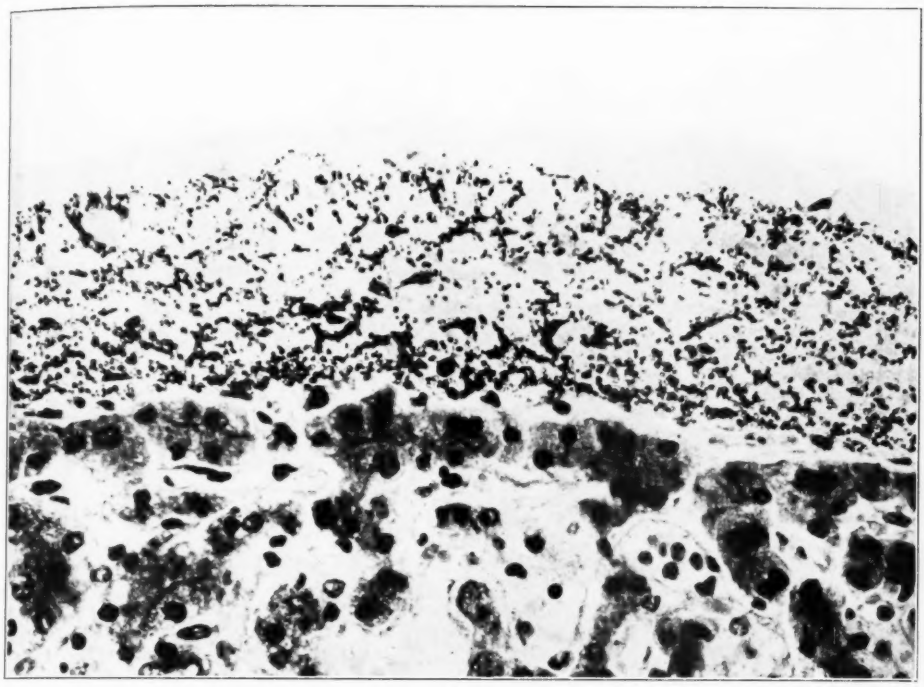
2

Gettler, Rhoads, and Weiss Generalized Argyria

PLATE 167

FIG. 3. Silver granules scattered throughout the connective tissue of the liver capsule, following the distribution of the elastic fibrils. × 500.

FIG. 4. Silver around a bile duct in the fibrous tissue of a portal area of the liver. × 500.



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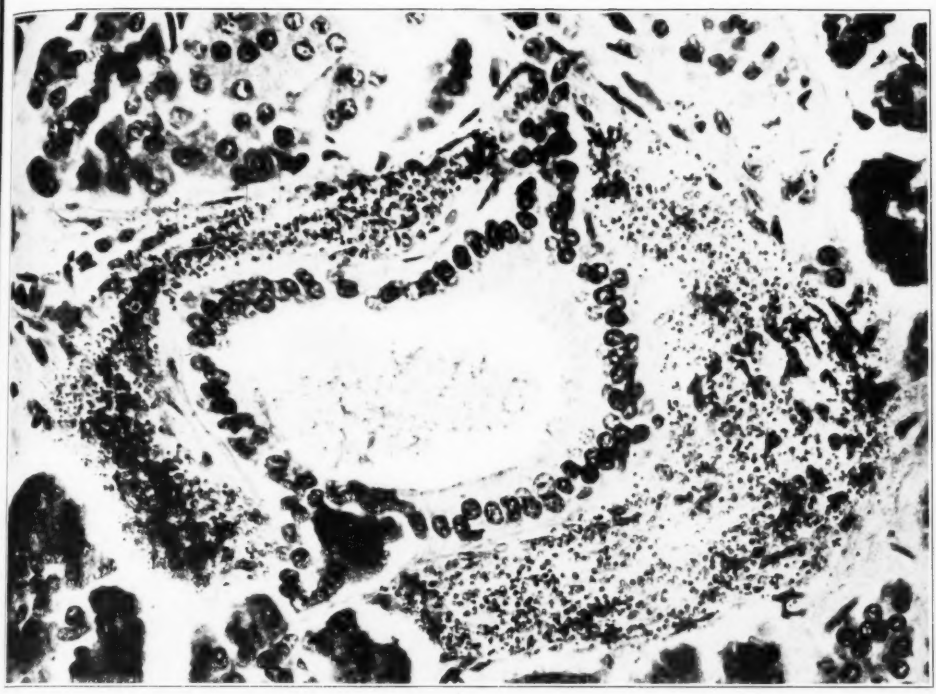
4

Gettler, Rhoads, and Weiss Generalized Argyria

PLATE 168

FIG. 5. Granules of silver in the periductular connective tissue of the pancreas. × 500.

FIG. 6. Stomach showing metal granules distributed irregularly through the muscularis and massed in the connective tissue close to the epithelium of the glands. × 500.



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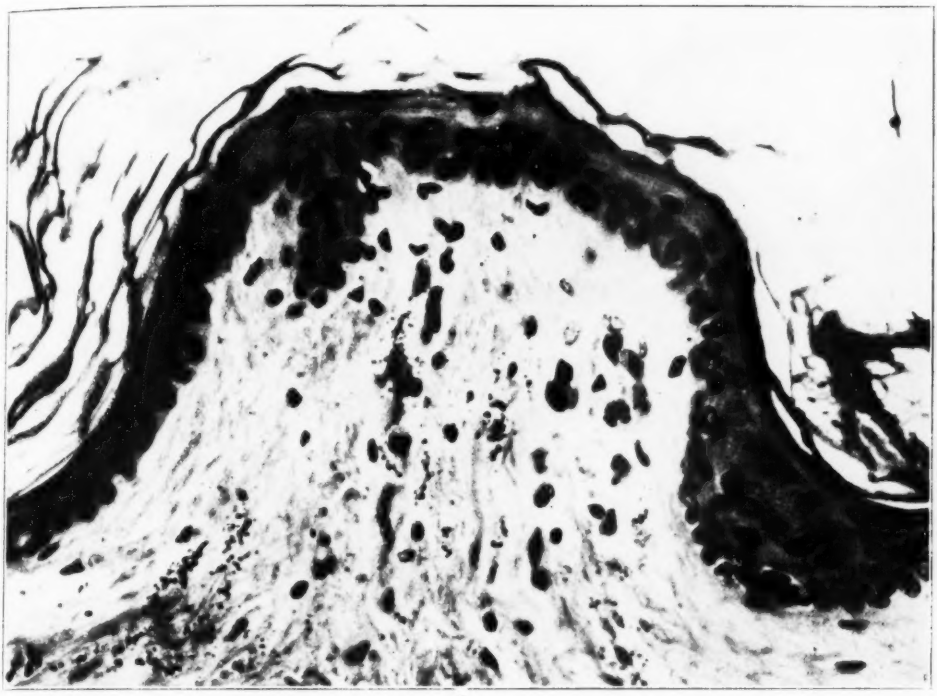
6

Gettler, Rhoads, and Weiss Generalized Argyria

PLATE 169

FIG. 7. Skin with silver particles in groups in the corium.

FIG. 8. Coil glands of the corium demonstrating metal in the connective tissue adjoining the epithelium. × 500.



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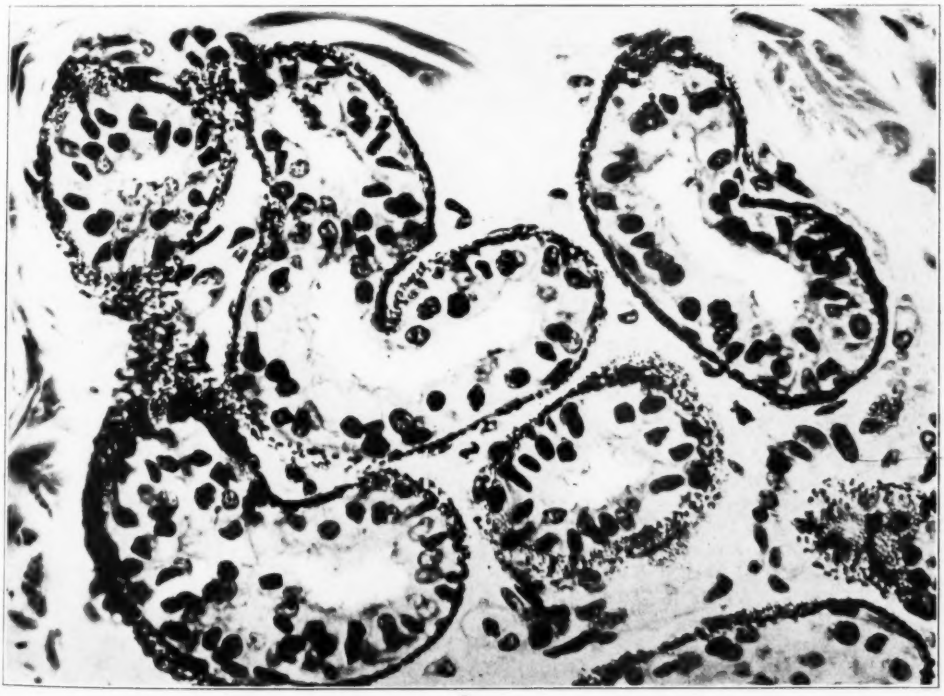

8

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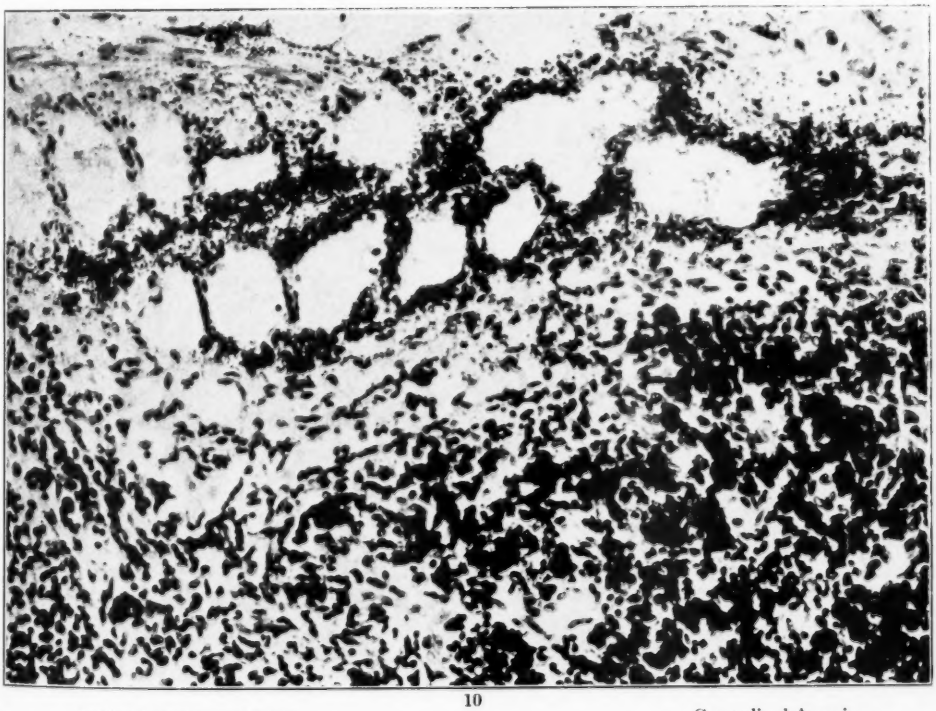
PLATE 170

FIG. 9. Heart muscle with silver granules in the fibrous tissue between the muscle fibers. × 500.

FIG. 10. Lymph node showing much silver deposited around lymphatics outside the capsule and also within the pulp. × 250.

9



10

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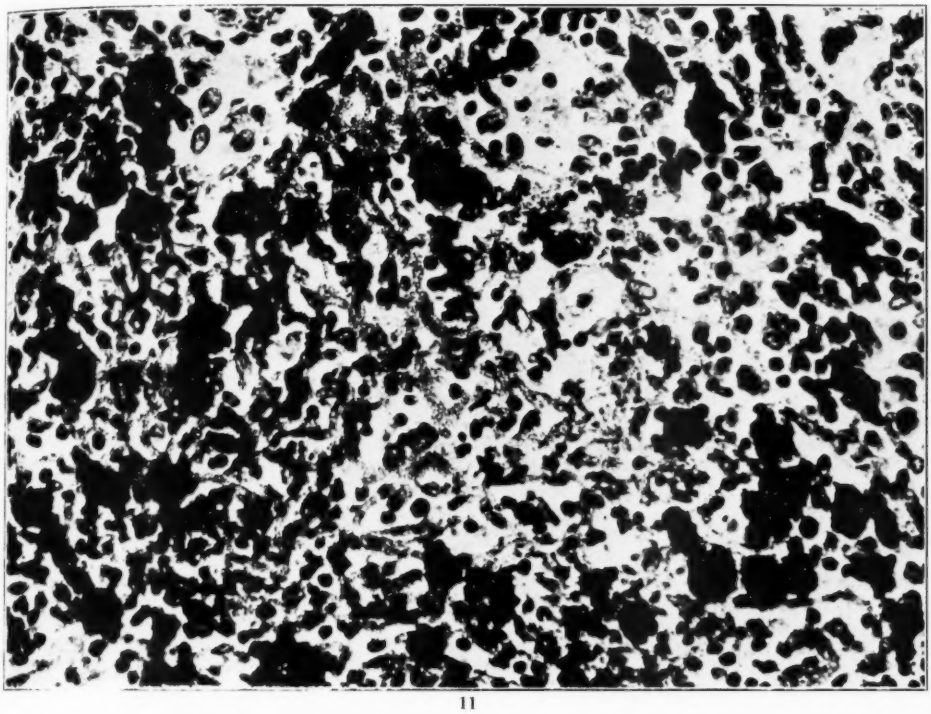
PLATE 171

FIG. 11. Lymph node with rows of silver along the collagen fibers marking out the supporting reticulum of the organ. There are also large masses of silver in phagocytic cells. × 500.

FIG. 12. Sinus of a lymph node showing phagocytic cells containing masses of silver. × 500.



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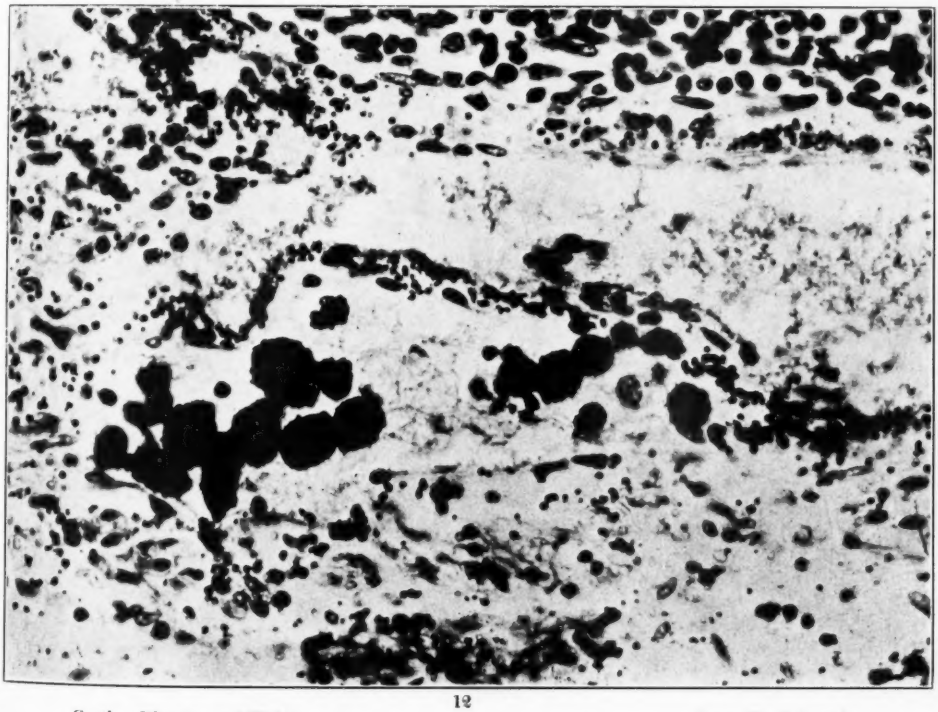

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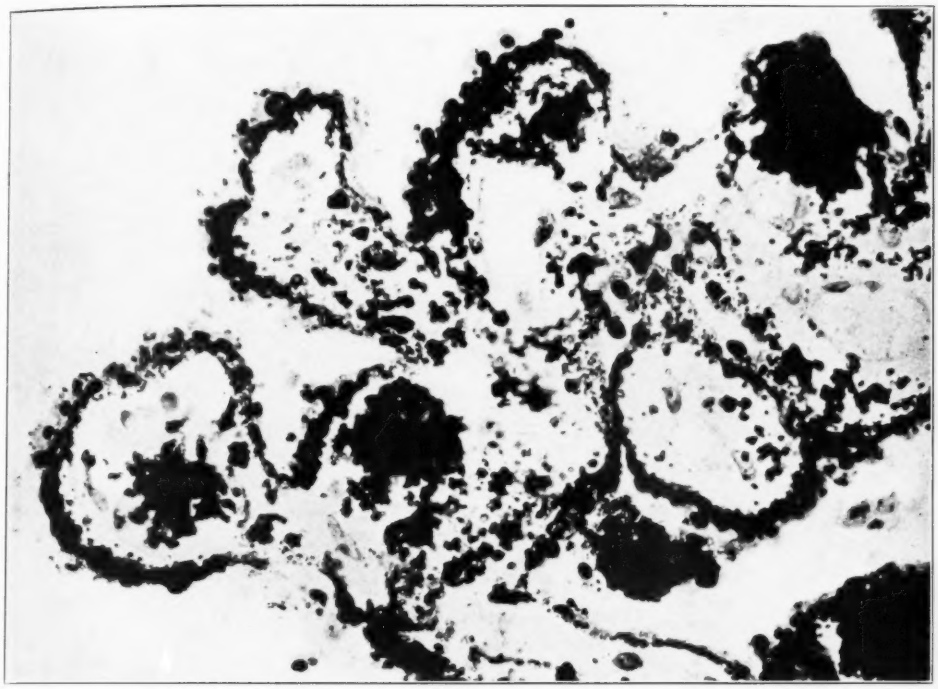
Gettler, Rhoads, and Weiss Generalized Argyria

PLATE 172

FIG. 13. Choroid plexus with scattered and massed silver particles in the connective tissue underlying the ependymal epithelium.

FIG. 14. Silver granules distributed along the delicate layer of collagen fibrils which underlie the endothelium of the cerebral capillaries. × 750.



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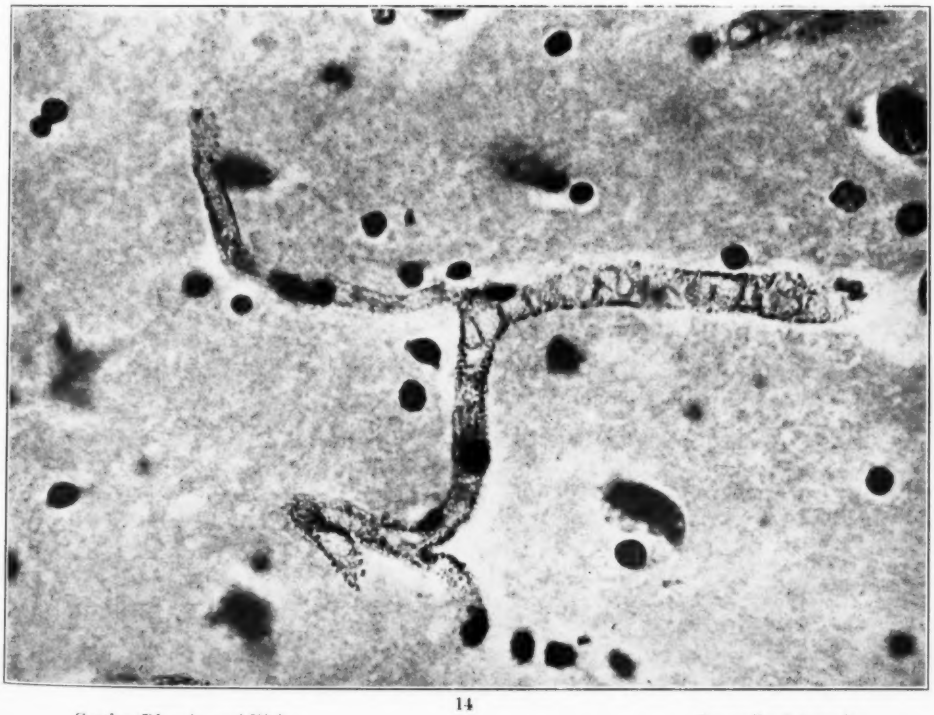

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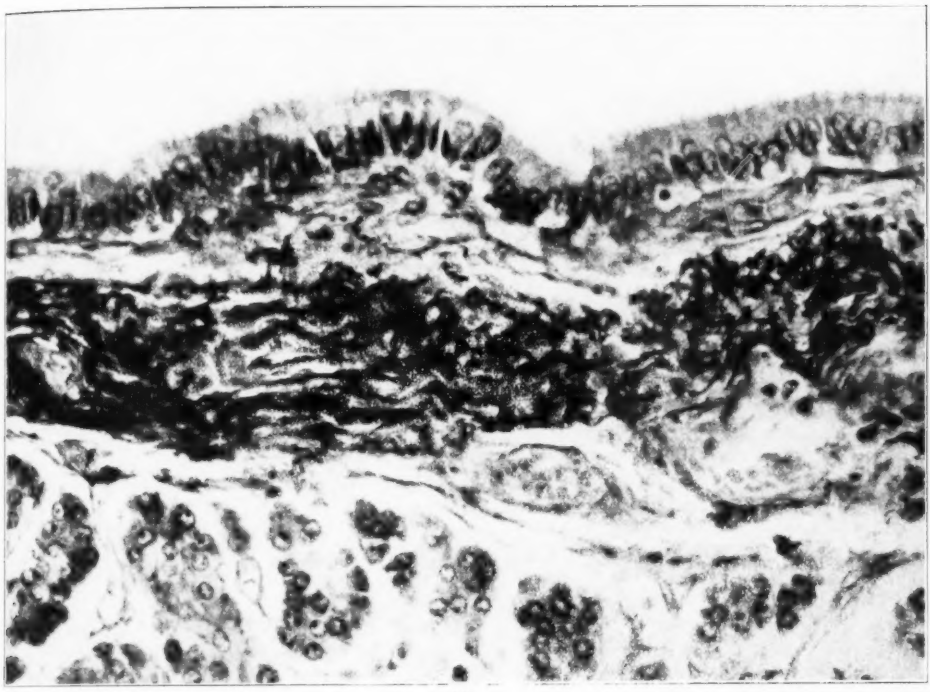
Gettler, Rhoads, and Weiss Generalized Argyria

PLATE 173

FIG. 15. Periductular connective tissue of pancreas stained for elastic tissue. This figure compared with Fig. 5 shows the close relation of the metal particles and elastic fibers in this area.

FIG. 16. An artery of the spleen stained for elastic tissue, which shows that here the silver is deposited in the adventitia outside the outer elastic membrane. × 250.



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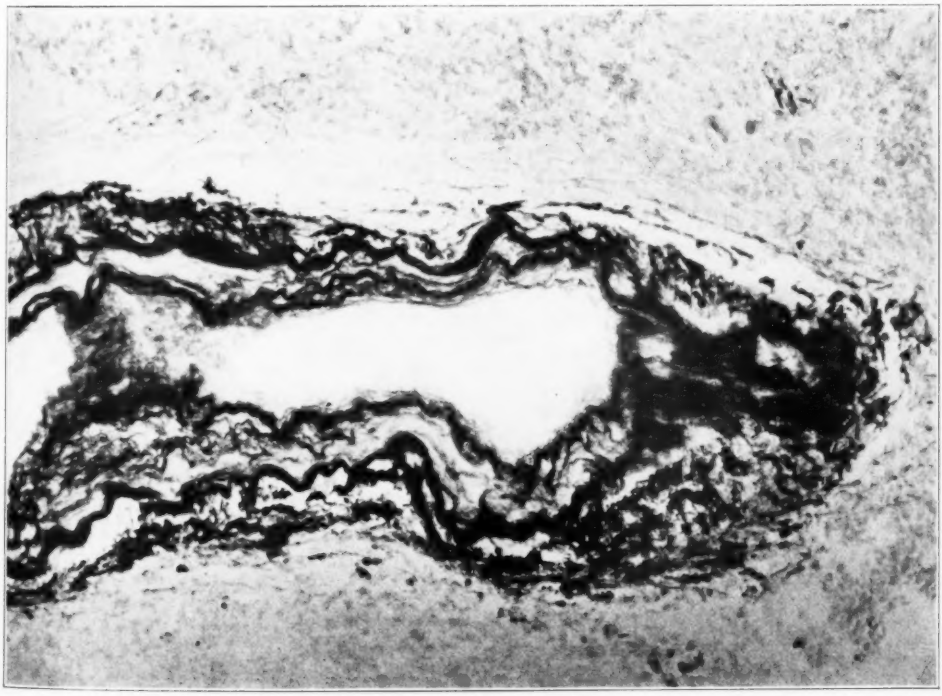

16

Gettler, Rhoads, and Weiss Generalized Argyria

A CASE OF PRIMARY MESENCHYMAL HEPATOMA: WITH NECROPSY *

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This case is of interest to both the clinician and the pathologist, for it presented obscure and misleading symptoms during life and was no less puzzling after a necropsy had been performed.

CLINICAL HISTORY

Present Illness: E. R., a white male baby of four months, was admitted to the pediatric service of the Cincinnati General Hospital on Aug. 23, 1926. The parents said that the child had become feverish and fretful a week prior to admission and that he had been somewhat constipated; no other symptoms were described.

Past History: A full-term, normally delivered baby, the child had been perfectly well since birth; he had never been exposed to contagion.

Family History: The father, mother and one brother were living and well; the mother had borne no other children besides these and there was no history of a miscarriage.

Physical Examination: The patient was a well developed, well nourished child, very restless, but apparently not acutely ill. The temperature was 101.6° F, the respiration 35 and normal, the pulse 140, irregular, but of good quality. Examination of the head, neck and chest failed to elicit anything abnormal; the abdomen protruded beyond the chest; bulging was present in the flanks. No abnormal pulsations were visible, there was no rigidity and but slight tenderness to palpation. A mass could be felt in the right upper quadrant, extending downward to just below the level of the umbilicus and to the left to within 3 cm. of it. It presented a notched, firm border, did not pulsate and the notch was felt just to the right of the umbilicus. Another mass occupied the left upper quadrant, extending downward to the iliac crest and to the right to within 3 cm. of the umbilicus. It had a sharply defined notch in its equally sharp border, felt just to the left of the umbilicus. These two masses were quite distinct, one from the other, the right being firmly fixed, the left one moving with respiration. There was an umbilical hernia and a double inguinal hernia. Aside from bowing of the legs, phimosis and slight icterus, nothing further could be determined.

Course in Hospital: The patient's condition grew steadily worse, despite continued breast feeding from its mother and six transfusions of blood from its father. Diarrhea developed and the temperature rose to 104° F, where it remained for a day or two before the child's death.

Laboratory Findings: A blood culture was negative.

* Received for publication May 18, 1927.

Urine: Albumen ++, otherwise negative.

Blood: 8/23/26. White blood cells, 30,000; polymorphonuclears 7 per cent; lymphocytes, 89 per cent; unidentified, 4 per cent. Anisocytosis, poikilocytosis, platelets absent.

8/28/26. Red blood cells, 1,784,000; white blood cells, 9,200; polymorphonuclears, 15 per cent; lymphocytes, 85 per cent.

8/29/26. Red blood cells, 1,790,000; hemoglobin, 50 per cent Sahli.

9/5/26. White blood cells, 10,400; polymorphonuclears, 4 per cent; lymphocytes, 89 per cent; mononuclears, 2 per cent; pathologic cells, 5 per cent; hemoglobin, 50 per cent Talquist. Occasional normoblast and megaloblast, few stippled cells, marked anisocytosis and poikilocytosis, platelets definitely diminished.

9/10/26. Red blood cells, 2,850,000; white blood cells, 11,700; platelets, 30,000 per cmm.; hemoglobin, 55 per cent Talquist.

Stool — Negative for parasitic ova.

Roentgenologic Examination: Heart outline somewhat enlarged, liver and spleen definitely so, otherwise negative. (Fig. 1.)

Clinical Diagnosis: Congenital lues, lymphoid leukemia, thrombocytopenic purpura and rachitis.

Necropsy Report

A necropsy was performed by Dr. Don F. Deeter, resident pathologist, seven hours postmortem. The child is definitely jaundiced, its skin lax and dry, the body somewhat emaciated. Nothing of note is observed previous to opening the abdomen.

Abdomen: Upon opening the peritoneal cavity, a rather large quantity of clear, amber fluid is evacuated. The liver reaches to the right anterior superior iliac spine and the spleen projects several centimeters below the left costal margin. The mesenteric lymph-nodes are slightly enlarged.

Spleen: This weighs 35 gm. and is large, purplish, and shows several small grayish points on its surface. The section-surface is smooth, fairly firm and purplish red; it drips much blood. The follicles are so obscured by the pulp as to be practically invisible.

Liver: The liver is large and weighs 275 gm. Its surface is everywhere studded with small grayish yellow areas averaging 1 to 2 mm. in diameter and projecting slightly above the surface, beneath the capsule. On the section-surface, similar grayish yellow areas are set off from the dull, light brown parenchyma, whose markings are diffuse and obscure. These tubercles are often softened at their centers, as though necrotic. One of them, much larger than the rest, measures approximately 1 cm. in diameter. The gall-bladder is not remarkable.

Gastro-Enteric: There are a few superficial ulcerations or erosions in the gastric mucosa; they average about 1 to 2 mm. in diameter. There is some congestion of the lower ileum and its Peyer's patches are somewhat swollen and prominent.

Other Organs: Nothing remarkable is noted in the case of the kidneys, pancreas, testes, urinary bladder or ureters.

Diagnoses: Multiple gummata of liver, congestion of spleen, ulceration of gastric mucosa, ascites, jaundice, umbilical and double inguinal hernia and rachitis.

Microscopic Report

Technic: Sections of various organs were made in paraffin and stained by routine procedure with Harris' hematoxylin and eosin; in addition, liver and bone marrow sections were impregnated with silver-ammonium carbonate and counterstained by Van Gieson's method; sections of the liver were also stained with Mallory's phosphotungstic acid hematoxylin, carbol-fuchsin and Levaditi's silver method.

General Findings: In the case of the heart, pancreas, testes and suprarenals, nothing of interest is encountered; the kidneys show a well developed tubular nephritis, with marked granular and albuminous degeneration, limited to the convoluted tubules.

Thymus: This shows an unusual atrophy, in that it is composed chiefly of epithelial elements and there is a marked dearth of the normal cortical lymphocytes, with a corresponding prominence of the thymic reticulum cells. The thymic corpuscles are either rudimentary, or show marked degeneration with necrosis at their centers, without any cellular reaction. Many of them have been transformed into thin-walled epithelial vesicles containing a little granular débris.

Spleen: There is pronounced passive congestion that floods the venous sinuses and renders them very prominent, at the same time compressing the splenic corpuscles until they assume insignificant proportions. The sinuses and pulp spaces are thronged with many large, actively phagocytic cells whose cytoplasm is filled with hemosiderin, fragments of erythrocytes and leucocytes, and sometimes entire cells — chiefly polymorphonuclear leucocytes. So numerous are these phagocytes that the picture reminds one of typhoid fever,

but the distribution of the phagocytes, the type of cell they ingest and their general appearance, are quite different. There are masses of cells resembling myeloblasts and myelocytes that, for this reason, indicate myeloid metaplasia.

Lymph Nodes and Lymphoid Tissue: These, too, are atrophic and show a very noticeable reduction in the number of microlymphocytes present; in place of the normal lymphoid follicles, there are aggregations of macrolymphocytes, some of them in mitosis and many of them showing pathologic transformations into large, irregularly staining cells, often with lobulated nuclei and dark cytoplasm. Some of these are very reminiscent of the Dorothy Reed, or Sternberg, giant cells of the Hodgkins' nodes. The central lymph sinuses and the capillaries of the nodules are much dilated and contain large numbers of phagocytes; and fairly large numbers of pale, distorted erythrocytes are found in the vessels and scattered through the lymphoid tissue. Apparently, some process involving the destruction of microlymphocytes, together with a compensatory hyperplasia of their parent cells, has been at work. The lymphoid tissue of the Peyer's patches and intestinal submucosa, on the other hand, is hyperplastic and contains the usual, or a somewhat increased number of microlymphocytes.

Bone Marrow: Sections from the costal bone marrow show some fairly normal fields and, in contrast to these, others are encountered that are strikingly altered. There are sections that are almost entirely pathologic in their composition (Fig. 2) the marrow being invaded by large numbers of large, pale, irregularly outlined phagocytic cells that are, apparently, invading, devouring and replacing the bone marrow. These cells often contain fragments of leucocytes, erythrocytes, or pigment; they are polyhedral rather than of rounded outline, their cytoplasm is vacuolated, their nuclei tend to be vesicular and reniform. They are not only identical, at least in their morphology, with the cells to be described in the case of the liver, but they are imbedded in and intimately associated with a reticulum that is identical in its appearance with that of the tumors. Owing to unevenness of the bone sections, it is impracticable to photograph the silver impregnations.

Microscopic Findings in the Liver

General: The parenchyma of the organ is compressed and distorted by a growth of new tissue in the periportal areas, or "triads." There is a marked fibrous tissue reaction to the presence of this growth, with consequent interference with the secretion of bile, which is found dammed back in the bile capillaries and the liver cells. Many phagocytes show greenish brown, finely divided particles of pigment in their cytoplasm. The central areas of the lobules are markedly congested and somewhat degenerated.

The New Growth: In the periportal areas are collections of cells quite foreign to this situation (Fig. 3). They are of irregular size and shape, pale, often somewhat vacuolated and usually discrete, arranged either loosely, or in rambling cords, but not in epithelial complexes suggesting alveoli. Sometimes they rim spaces, but even then have very little resemblance to glands. Often they are merely aggregations of cells, each separate from its neighbor and presenting the appearance of the "epithelioid cells" of tuberculosis. In such cases, the aggregations are fairly sharply circumscribed and form spherical, somewhat encapsulated groups; they often show little delimitation and invade the liver parenchyma in their neighborhood by way of the sinusoids. Numbers of leucocytes are often intermingled with these cells, which frequently give the growth the appearance of some sort of granuloma.

The nuclei of the tumor cells are reniform, rounded, or squash- or club-shaped; they are vesicular and pale, with a well defined nuclear membrane and a very poorly defined, or no nucleolus; they are sometimes multiple, two or three presenting in a single cell. Very few mitotic figures are found after most careful and prolonged searching, but as they are in smaller cells it is questionable whether these are tumor cells, or elements of the stroma. A high power photomicrograph of the type cell is reproduced (Fig. 4).

One's first impression, while examining this tumor, is that it has an epithelial origin; for this reason careful observations were made to determine whether or not transitions between the tumor and the liver cords could not be found. Wherever the tumor invades the liver these cords become swollen and degenerated, their cells vacuolated and dissociated, but their nuclei retain their typical round outline and prominent nucleoli. Nucleoli are seldom observed in

the tumor cells. Furthermore, the only cells that resemble those of the tumor with any exactness are found in the walls of the sinusoids, or free in their lumina rather than associated with epithelium, and they are obviously Kupffer cells. Their nuclei are perfectly similar to those of the type cells and their hyaline, pale cytoplasm resembles that of the tumor, which is quite unlike the deeply staining, granular cytoplasm of the liver cords. The liver epithelium, moreover, is often bile-stained and contains large droplets of inspissated bile and encircles dilated bile capillaries; this is not noted in the tumor cells. Pigmented phagocytes lie isolated and included in masses of the tumor, but exactly similar cells are observed in the liver sinusoids; they are quite different in their appearance from the bile-stained epithelium. Where the tumor invades the liver, it does so by way of the sinusoids, rather than replacing liver cords.

As stated, there is a marked fibrous tissue reaction to the presence of the tumor, the stroma (or better, matrix) being chiefly composed of reticulum, although there is a great deal of collagenous connective tissue in the larger, more diffuse areas. This reticulum is so intimately associated with the type cells, not tending to demarcate alveoli, that the question as to whether it is not matrix, rather than stroma, is immediately raised (Fig. 5). In the writer's experience carcinomas very rarely and non-malignant tumors practically never show an invasion of their cell complexes by the stroma; such an invasion always suggesting mesodermal origin of the type cell (Foot and Day [1]).

Cell inclusions are frequently observed, although the frank phagocytosis exhibited by the strikingly similar cells in the bone marrow is not found. This might be explained by the firm, closely bound surrounding tissue in the one case and the loosely associated marrow elements in the second; it would be as easy for phagocytic cells to take up myeloid elements as it would be difficult and unusual for them to phagocytose fibers or liver parenchyma.

In order to rule out syphilis and tuberculosis, Levaditi and Ziehl-Neelson preparations were made and examined with quite negative results. Gram and methylene blue stains were equally unenlightening.

Microscopic Diagnoses: Primary mesenchymal hepatoma, probably metastatic to costal bone marrow; chronic passive congestion of liver, with bile stasis and cirrhosis; passive congestion of the

spleen, with myeloid metaplasia; atrophy of thymus and mesenteric lymph nodes.

Discussions

This is, then, a case of multiple tumors of the liver with an invasion of the neighboring bone marrow that strongly suggests metastasis, owing to the similarity of the cells in each instance. At first glance one is inclined to diagnose such a case as a granuloma of some sort, tuberculous or luetic. This was the provisional diagnosis at necropsy. But our microscopic examination throws us back upon a diagnosis of neoplasia. Having arrived there, with what type of tumor are we dealing? Primary adenoma of the liver is not uncommon in children, in a rather diffuse and multiple form; but can we consider this an adenoma? Can it, indeed, be considered to be of an epithelial nature? The type ceil suggests epithelium, but it also suggests mesodermal origin.

Arguing against an epithelial origin we may point out that:

(*a*) There is no tendency for the cells to form glands or definitely coherent alveoli.

(*b*) There is great similarity between the cells of the tumor and the phagocytic interlopers in the costal bone marrow.

(*c*) There is a tendency for the cells to be multinuclear.

(*d*) They are usually discrete and very intimately associated and intermingled with reticulum, which is more typical of reticulo-endothelial, than it is of epithelial structures.

(*e*) They resemble Kupffer cells more closely than they do hepatic epithelium.

(*f*) They invade the liver tissue by way of the sinusoids, rather than replacing the liver cords.

In favor of an epithelial origin of the tumor the following points may be noted:

(*a*) Tumors corresponding to this type of neoplasm are usually epithelial.

(*b*) The cells of this tumor resemble epithelium closely enough to be termed "epithelioid," they show some tendency to form cords and a very slight one to line spaces.

(*c*) Ducts are occasionally seen in the tumor, but these could be construed as representing surviving bile ducts.

It is quite possible that there is no relationship between the cellular aggregations in the bone marrow and the tumor in the liver; the former are composed of much larger cells, as may be seen in the illustrations, which were taken at the same magnification. The increase in size, however, could be explained on the ground of compression in the dense tumor and lack of this in the loose marrow. Metastasis, in the absence of numerous mitoses, is not as readily assumed as it could be were there many of these; but the tumor has grown readily enough throughout the liver and could, therefore, set up subsidiary growths outside of that organ. That this tumor is malignant is indicated by the poor differentiation of its type cells, by their diffuse and infiltrating growth and the possibility of metastasis to the ribs; that it was clinically malignant is amply proved by the fact that it killed the patient.

The most comprehensive description of these tumors will be found in Ewing's Neoplastic Diseases.[2] He lists primary tumors of the liver under the following heads: (*a*) Solitary adenoma, (*b*) Primary massive liver cell carcinoma, (*c*) Multiple liver cell carcinoma or hepatoma, and (*d*) Carcinomatous cirrhosis; or, multiple adenoma, carcinoma, or hepatoma with cirrhosis. The tumor under discussion might fall into the last category, were we certain of its epithelial nature. Ewing mentions the fact that Geraudel considers some of these to be of mesodermal origin, but dissents from this view on the grounds that the liver "is derived from exactly the same endodermal bud as the bile ducts, and the only part of the parenchyma which is of mesodermal origin is the system of blood vessels."

If our tumors, then, be not of endodermal origin, they are probably derived from the vascular primordium of the liver, or from its appendages which produce the hepatic stroma. For the reasons already given, it seems to the writer that we are dealing with a primary mesodermal tumor of the liver which has grown diffusely, either arising simultaneously in many parts of the organ, or rapidly seeding itself out from the largest nodule discovered at necropsy and possibly metastasizing to the neighboring ribs. Such a diagnosis may seem presumptuous, in the face of tradition, but we have ample evidence that the Kupffer cells may form large aggregations in tuberculosis, and in other conditions. The experimental work on tuberculosis of the liver has shown this to be true (Evans, Bowman, and Winternitz,[3] Foot,[4] Kockel,[5] and others). Why should these cells

not be capable of undergoing somewhat similar changes under the influence of neoplastic stimulation and become transformed into actively growing tumor masses? This hypothesis will bear consideration; it is only by publishing such cases and inviting free criticism and discussion, that we can arrive at any definite conclusion as to their true nature.

NOTE: Personal correspondence with Dr. Ewing indicates unmistakably that he considers this case to be one of multiple adenoma of the liver. Although he examined the sections from the liver, he did not see those from the marrow, which attracted attention only after the liver sections had been studied and sent on to him.

SUMMARY

A case of multiple tumors, occurring in a boy of four, is described from the clinical and pathologic points of view, the latter being stressed. The tumors simulate multiple granulomata, possibly tuberculous or luetic, but when examined more closely are found to be neoplastic. They are rich in reticulum and are found to invade almost all the periportal tissue of the liver. Similar cells and reticulum are found in the neighboring costal bone marrow, which are probably metastases to that tissue, although this is not proved. The nature of the growth is discussed, and it is concluded that it probably had its origin in the mesodermal primordium of the liver; the possibility of its being of epithelial origin has not been overlooked.

Photomicrographs by Mr. J. B. Homan (Dept. Medical Art, College of Medicine, University of Cincinnati) and the author.

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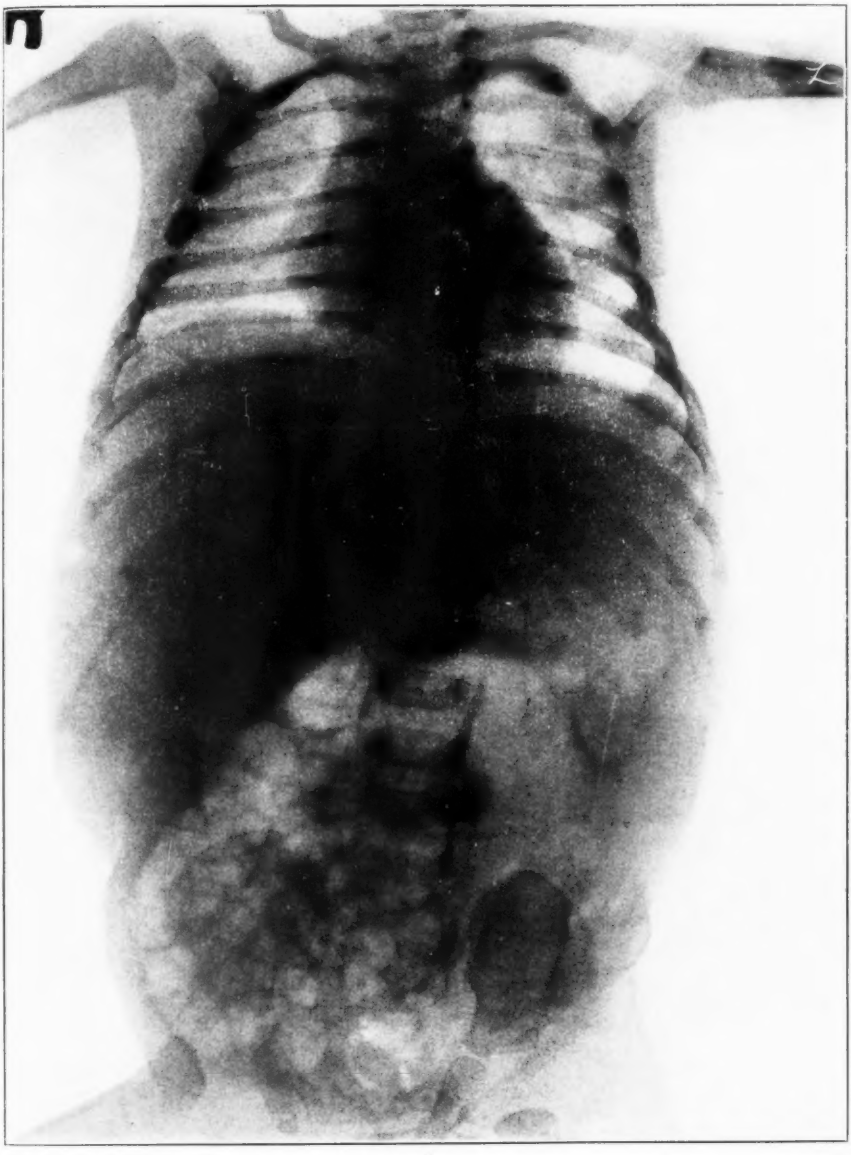
DESCRIPTION OF PLATES

PLATE 174

FIG. 1. Roentgenogram of the patient, showing enlarged liver, spleen and heart; no metastasis visible in ribs.



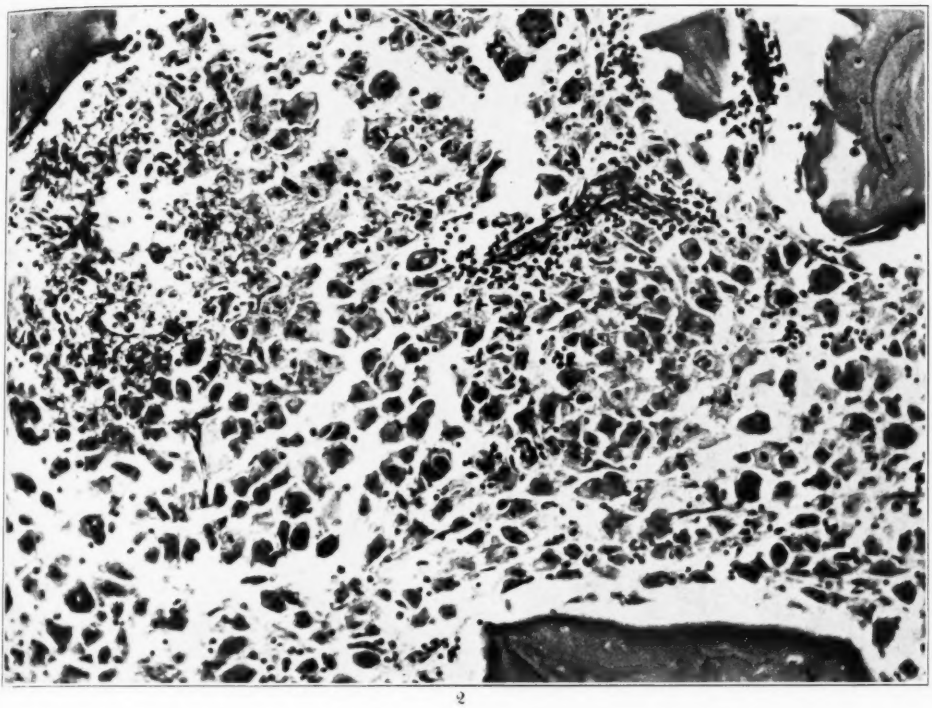
1

Foot Primary Mesenchymal Hepatoma

PLATE 175

FIG. 2. Photomicrograph of the bone marrow, showing invasion by large numbers of phagocytes, possibly a metastasis. Hematoxylin-eosin. × 200.

FIG. 3. Photomicrograph of the tumor and the liver tissue at its margin. Note the lawless distribution of tumor cells. Hematoxylin-eosin. × 200.



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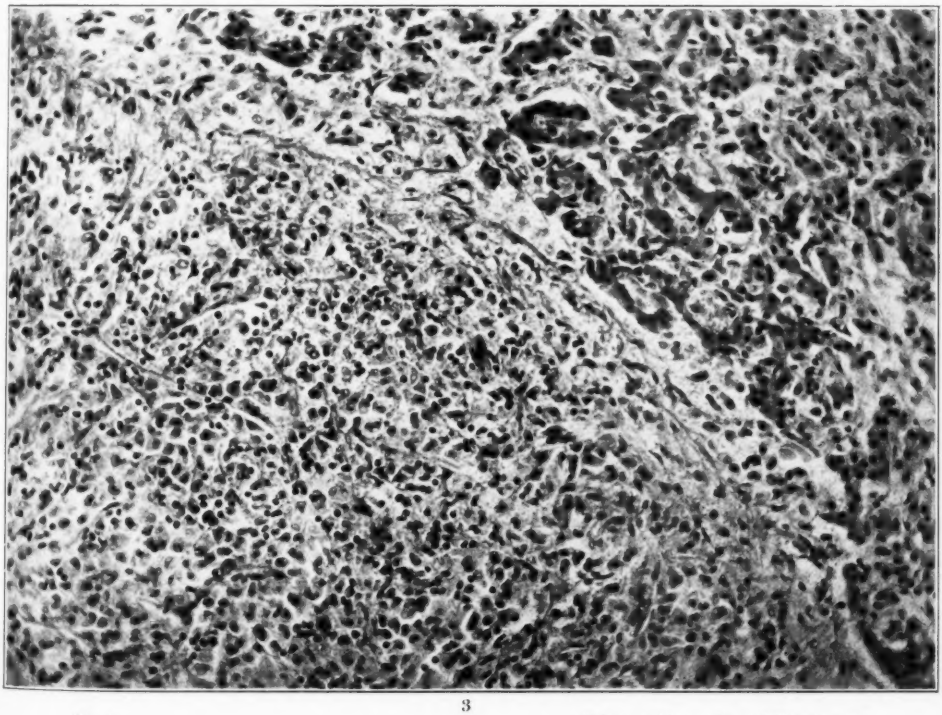


3

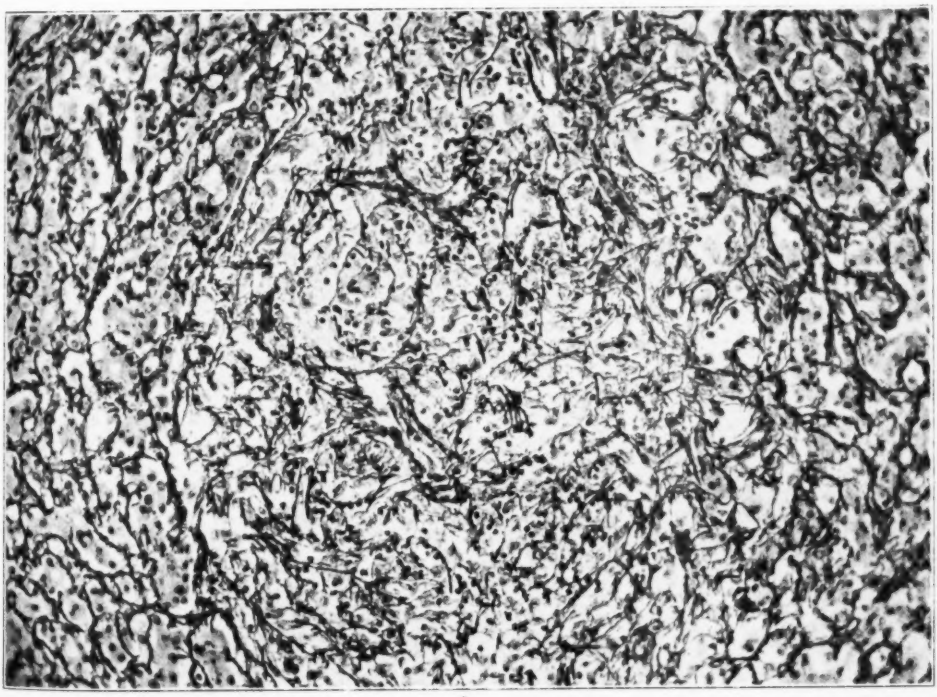
Foot Primary Mesenchymal Hepatoma

PLATE 176

FIG. 4. Photomicrograph of a field in the tumor, to show the distribution of reticulum and the type cells. Silver-ammonium carbonate-Van Gieson technic. × 800.

FIG. 5. Photomicrograph of a portal area completely replaced by tumor tissue. Note distribution of reticulum and dissimilarity of the tumor and liver cells. Silver-ammonium carbonate-Van Gieson technic. × 200.

4



5

Foot Primary Mesenchymal Hepatoma

UNIV. OF MICH.

SARCOSPORIDIAL INFECTION OF THE MYOCARDIUM IN MAN *

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The first instance of sarcosporidial infection was discovered in mice by Miescher [1] in 1843, who described white filaments running parallel with the direction of fibers of voluntary muscles. Since that time sarcosporidiosis has been found very commonly in cattle, horses, sheep and pigs and also in various other mammals, as well as birds and reptiles. Wenyon [2] gives a complete list of the animals in which this parasite has been found together with the different species, but it is possible that they are all of the same species, taking slightly different forms in the different hosts. Although these protozoa are usually non-pathogenic even in very heavy infections, one form, the *S. Muris*, is lethal to mice and at times may cause fatal epizoötics in sheep.

The sarcosporidia are characteristically surrounded by a membrane or capsule, which in the younger cysts, cannot always be demonstrated. In the older ones this becomes quite definite and occasionally appears to be radially striated. It has not yet been decided whether this surrounding membrane develops from the parasite itself, or is formed about it by the adjacent cytoplasm. Growth of the cysts occurs in the periphery. At the same time the central portion may become necrotic. In the older sarcocysts thin trabeculae often run from the capsule through the interior, forming chambers which contain the spores. These spores vary in shape, but usually are kidney- or sickle-shaped and measure 10 to 15 microns in length.

The natural mode of transmission of this parasite is not known, but the infection has been produced in mice by Theobald Smith [3] by feeding them infected mouse flesh. The sarcocysts could not be demonstrated in these mice until forty-five days after the infected material had been administered to them. After this time about 63

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per cent of the experimental animals were found to harbor this parasite. More recently Darling [4] has been able to transmit this infection to guinea pigs by similar methods, but this does not account for the manner in which the parasite gains entrance to hosts that are strictly herbivorous. In further experiments Theobald Smith [5] has proved that this organism was not transmissible from parents to their offspring.

Sarcosporidia in the human were first described by Rosenberg [6] in 1892, who found small round or oval refractile bodies in a cyst in the papillary muscle of the left ventricle in a woman of 40 years, dying of pleuritis and endocarditis. According to Fantham, Stevens and Theobald [7] there is some doubt about this case being one of true sarcosporidiosis. The first authentic instance of the appearance of this parasite in man was reported by Kartulis [8] in 1893, who found Miescher's cylinders of various sizes in the muscles and possibly in the liver of a Sudanese who succumbed to multiple abscesses of the liver and abdominal muscles. Baraban and Saint-Remy [9] found undoubted parasites in the laryngeal muscles of a man who was executed. Darling reports two cases of sarcosporidiosis in man. The first [10] was in a piece of biceps muscle obtained from a negro working in the Canal Zone and suffering from typhoid fever. In a biopsy performed four months later no parasites were seen, so it is possible that they are only transient invaders of the human host. Darling's second instance [11] was in an East Indian who died of malaria, and sarcocysts were found in sections of the muscles of the tongue. Cone [12] reports a case of multiple bone cysts from which he recovered bodies resembling the sarcosporidium, as well as yeasts. After feeding rats some of the infected material he found similar bodies in their muscles but it seems possible that all the bodies described by him were yeasts. The last case to which we have found reference is that of Manifold,[13] published in 1924. In sections of heart muscle three parasitic cysts (A, B, and C) were found, and two others in sections of tissue in the vicinity. Numerous other blocks were examined later without finding additional parasites, so the infection, it was inferred, must have been slight. The lining membrane of the cysts stained well, but no trace of hair-like processes could be seen. The cysts contained the usual sickle-shaped spores, which were evenly distributed and did not appear to be packed into spore chambers. No evidence of a reticulum could be made out. The sur-

rounding muscle appeared quite healthy in two of the cysts, but was somewhat hyaline in the third.

The dimensions, in comparison with Darling's case, are given in the following Table: In the last column the measurements of the parasites in our case are appended.

	Manifold's case			Darling's case	Lambert's case
	Parasite A	Parasite B	Parasite C		
Sporozoan:	*mm.*	*mm.*	*mm.*	*mm.*	*mm.*
Length	.057	.045	.034	.084	.082
Width	.045	.039	.026	.027	.031
Spores:					
Length	.01092	.01082	.01092	.00425	.0072
Width	.00156	.00136	.00156	.00175	.002–.0025

Report of Case: R. B., age 32, negress, housewife, married, born British West Indies.

History: Admitted to the hospital Sept. 18, 1926, she died Sept. 19, 1926 (history from sister). Always well until four months before admission when she commenced having headaches, anorexia, frequency of urination and blurring of vision, all of which persisted up to ten days before admission. At that time she became much worse, being forced to bed by transitory blindness, continued severe headaches, pain in back of neck and intermittent pain in kidney region. On the night of admission she became completely disoriented.

Physical Examination: Temperature 99.2° F; Pulse, 120; Respiration, 20; Blood pressure, systolic 270, diastolic 170.

A poorly developed negress, active and argumentative. Pupils negative. Eyegrounds showed white exudate and hemorrhages. Heart not enlarged. Soft systolic apical murmur. Aortic second sound markedly accentuated. Pulse strong. Vessels thickened, not tortuous. Deep reflexes more marked on left than on right.

Laboratory Findings: Hemoglobin, 100 per cent; red blood cells, 7,300,000; white blood cells, 12,200; polymorphonuclears, 78 per cent; lymphocytes, 12 per cent; endothelials, 10 per cent. Urine: Specific gravity, 1014; albumen, heavy trace; no casts. Some white blood cells in clumps. Lumbar puncture: fluid under greatly increased pressure. Cells: lymphocytes, 30; red blood cells, 310; globulin, slightest possible trace. Wassermann: negative. Colloidal gold, 0011221000. Protein 75 mg. per 100 cc. Blood urea .55 gms. per liter. CO_2, 45.7 vols. per cent.

Course: The day of admission she developed a very stiff neck with suggestive Kernig on the right, right deep reflexes increased and right Babinski. The following afternoon she died with failing respirations and weak, irregular heart action. Blood pressure over 300.

Necrospy Report

Anatomic Diagnoses: Acute and chronic arteriolitis; chronic nephritis (arteriolar); cardiac hypertrophy (left ventricle); acute endocarditis, mural (rheumatic); lobular pneumonia; hemorrhage into cerebellum; sarcosporidiosis of heart; fibromyoma of uterus; hydrosalpinx; sclerosis of pulmonary venules; fibrous pleural and peritoneal adhesions.

The anatomic diagnoses sufficiently state the findings in the case so that only the heart will be described.

Heart

Gross Description: Weight 360 gm. The heart is enlarged, the enlargement being due chiefly to hypertrophy of the left ventricle which is firmly contracted; the right ventricle and auricle are dilated. There are a few small epicardial hemorrhages on the surface of the right auricle. The myocardium is of the normal red-brown color except on the septal portion of the left ventricle where there are numerous subendocardial hemorrhages of considerable size. The endocardium is smooth and glistening throughout. The valves are thin and delicate except for a small atheromatous plaque in the aortic leaflet of the mitral valve. The coronary arteries show slight atheroma.

Microscopic Examination: Sections from the left ventricle show some hypertrophied muscle fibers, some with vacuoles and some that are fragmented. Throughout the myocardium are a few small areas of fibrosis, and about the blood vessels there is some lymphocytic infiltration. Immediately beneath the endocardium are a number of polygonal cells with rather basophilic cytoplasm and directed more or less vertically to the surface. In several places they are grouped into submiliary nodules which project above the surface and one of these is covered with a fresh deposit of fibrin. The walls of the blood vessels are somewhat thickened.

In sections from the interventricular septum are seen a few scattered parasites lying in individual muscle fibers. These fibers are swollen to about twice their natural size and stain more homogeneously than the other fibers in the sections. However, the striations can be seen faintly and the fibrils are easily distinguishable in the

sections stained with phosphotungstic acid hematoxylin. Situated in the center of each of these fibers is an oval body about which no capsule can be demonstrated. This mass is composed of groups of small light blue-staining sickle- or spindle-shaped organisms, measuring approximately 7 to 10 × 2 to 2.5 microns. In the center of each is a darker blue-staining nuclear portion that roughly takes the same form as the organism. In places these are arranged with their long axes pointing more or less in the same direction, although no trabeculae can be seen dividing the whole mass into compartments. Accurate measurements of these bodies cannot be made from the sections because of the difficulty in determining their exact outlines, as they do not lie in a single plane. The cysts themselves measure 82 × 31 microns.

The above finding is merely an accidental one. There were no symptoms during life which could be referred to this infection. As all the tissue was preserved before the microscopic sections were examined it was not possible to carry out any experimental work on the transmission of this parasite. However, it seems quite probable that it is some form of sarcosporidia, and in a rather early stage of its development, judging from the fact that no capsule can be seen surrounding the cyst. It differs from the majority of species previously described in the following characteristics: (1) In the absence of a surrounding membrane; (2) In the lack of demonstrable septa dividing the cyst into compartments; and (3) In the measurements, which though not carried out on fresh material, indicate that this form is smaller than those previously described. As no sections of skeletal muscle were taken for microscopic examination it is not known whether this infection was general throughout the whole body or merely confined to the myocardium. The case is reported as one of probable sarcosporidial infection of man, and is the second one on record in which the protozoa invaded the heart muscle.

I am indebted to Dr. Walter W. Palmer for permission to transcribe the clinical record of this case.

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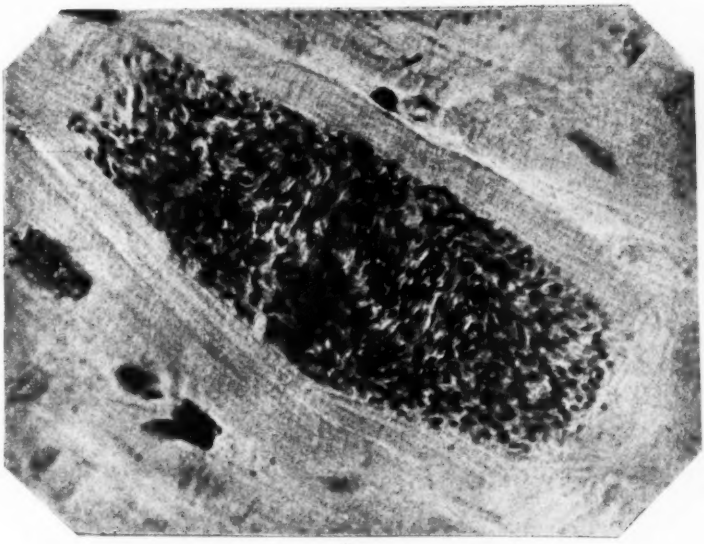
DESCRIPTION OF PLATES

PLATE 177

FIG. 1. Sarcosporidia in heart muscle fiber. Longitudinal section. × 1050.
FIG. 2. Sarcosporidia in heart muscle fiber. Cross section. × 1050.



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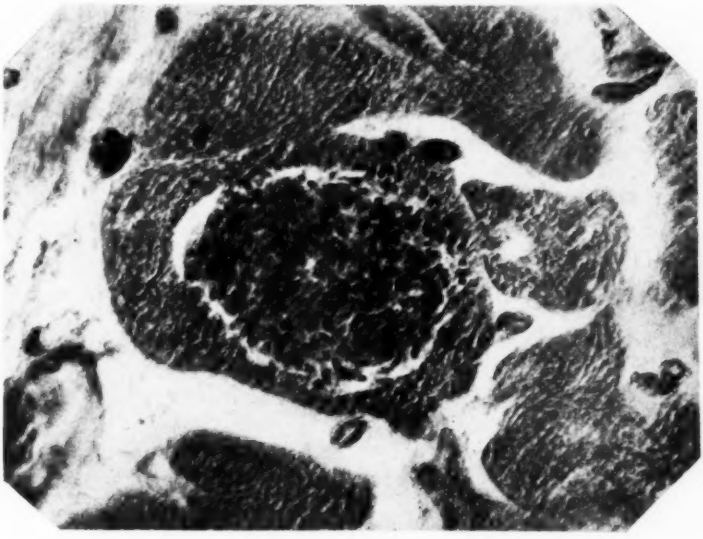

2

Lambert Sarcosporidial Infection of Myocardium

A COMPARISON IN NORMAL, THYROIDECTOMIZED AND HYPOPHYSECTOMIZED RATS OF THE EFFECTS UPON METABOLISM AND GROWTH RESULTING FROM DAILY INJECTIONS OF SMALL AMOUNTS OF THYROID EXTRACT *

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Although a very considerable number of reports have been published upon the administration of thyroid to laboratory animals, an interesting and important phase has scarcely been touched upon, for little or no work has been done with the thyroidectomized or the hypophysectomized animal as the test form. The effects of thyroid administration have been studied almost exclusively on the normal animal. Furthermore, except in the experiments of Cameron and Carmichael,[1, 2, 3] the amount of thyroid administered has not been in proportion to body weight, the same amount of thyroid having been given throughout each experiment. Consequently, as growth proceeded, the animals received relatively less and less of the gland substance. The results reported from thyroid administration, nevertheless, have been harmonious as regards its effect upon basal metabolism, which is increased, and upon certain organs, the adrenals, kidneys, liver and spleen, which show an enlargement. As regards growth, the results have been more variable, some reporting a retardation, others either no effect or a slight acceleration in the rate of growth.

We have been carrying on for some time the experimental administration of thyroid extract in three types of rats, the unoperated normal, the thyroidectomized and the hypophysectomized. In these experiments fresh thyroid extract has been administered daily by intraperitoneal injection, the dosage given being directly propor-

* Aided by grants from the Board of Research of the University of California.
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tionate to body weight. The intraperitoneal injection of the extract is less time-consuming than feeding, since the animal need not be watched to make certain that the thyroid is all consumed. In these experiments we attempted to give a dosage but slightly in excess of that necessary for a complete replacement therapy in the thyroidectomized animal (*vide infra*), a dosage which we could assume to be "physiologic" for this type. Although direct comparison of the hormonal content of our dosage with that of other investigators is impossible, yet it appears from the physiologic responses of the treated animals that our dosage is less than that heretofore employed. Nevertheless, it gave pronounced results with both thyroidectomized and hypophysectomized animals, effects which have been registered by measurements of basal metabolism, by studies of the specific dynamic action of injected amino acids, and by measurements of general body growth and organ weights.

While the results obtained with each experimental type of rat — the normal, the thyroidectomized and the hypophysectomized — have been of interest in themselves, these results, however, have proved of more interest when compared with effects obtained upon each of the other types. It, therefore, seemed best to bring the data together in one paper so that these comparisons might be emphasized.

Methods

The completeness of the thyroid ablations has been verified by a careful examination with a binocular dissecting microscope at necropsy and a subsequent study of serial sections through the entire laryngeal region. The hypophysectomies have been done by a method described briefly elsewhere (Smith [4]). A study of serial sections has shown that both the anterior and the posterior portions of the pituitary were completely removed in all instances.

The animals were weighed every three days. Every two weeks they were placed under deep ether narcosis in order to measure accurately their body and tail lengths.

The thyroid extract (suspension) for injection was prepared daily as follows: Fresh sheep thyroids freed from their sheaths were weighed, sterilized for ten minutes in fifty per cent alcohol, rinsed in saline, and ground with sand. They were then diluted in the proportion of 1 gm. of thyroid to 3 cc. of saline, and centrifuged for

twenty minutes. After trying various test dosages it was decided to inject daily, 0.02 cc. of this thyroid extract to each 25 gm. of body weight, a dosage used in all experiments reported here. Although care was used in securing accuracy in dilution and in administration, there was undoubtedly some variability in the amount of thyroid hormone administered from day to day, because of the variability of the hormonal content of the thyroids used in preparing the extract. Such variability was reduced by using glands from several animals for each batch of extract. Any variability, however, in the strength of the extract seemed less objectionable than using a commercial preparation, or even one such as thyroxin which is subjected to severe chemical treatment in its preparation. However, our preference for fresh gland extract rather than thyroxin may be unwarranted, for qualitatively the effects obtained with the injection of the two have been shown to be identical (Cameron and Carmichael [3]).

The measurements of respiratory metabolism were made with the apparatus recently described by Foster and Sundstroem.[5] The routine of a metabolism experiment is as follows: The rat, deprived of food for twelve to eighteen hours, is placed in the respiration chamber. Usually within thirty to forty minutes the animal comes to rest and sleeps. Two or three basal periods of twenty minutes each are obtained, after which the animal is taken from the chamber and receives an intraperitoneal injection of glycocoll, alanine or glucose.* (The glycocoll and alanine are given in 15 per cent solution to the amount of 1.5 grams per kilogram of body weight. Glucose is administered in 30 per cent solution to the amount of 3 grams per kilogram.) On being returned to the respiration chamber the animal becomes quiet, usually within thirty minutes, whereupon measurements are resumed in a series of twenty-minute periods.

The animal chamber is kept at a constant temperature (28.5°–29.5° C.), at which temperature the rat soon becomes drowsy, and in general with our animals not much trouble has been encountered in keeping the subjects quiet. The observer, however, watches the animal and discards any period complicated by movements of the animal.

* In harmony with Weiss and Rapport [6] but contrary to Liebeschütz-Plaut and Schadow [7] we find specific dynamic action of glucose and amino acids following parenteral administration.

Effects upon Basal Metabolism

The Unoperated Rat. As shown in Table 1, the average of forty-four observations of basal metabolism of normal untreated rats was 4.8 Cal. per kilogram per hour (maximum 5.7, minimum 4.1). This is considerably lower than the figures for the metabolism of fasting rats reported by Abelin [8] and his co-workers and by Goto.[9] It may

Table 1

Summary of Basal Metabolism Experiments

Group	Basal Metabolism					No. of observations
	Cal. per Kg. per hr.*			Mean as per cent of normal untreated animal	Mean of treated animal as per cent of untreated animal of each type	
	Max.	Min.	Mean			
Unoperated not injected	5.7	4.1	4.8	100	100	44
Unoperated injected	6.3	5.3	5.5	115	115	15
Thyroidectomized not injected	4.0	3.2	3.5	73	100	15
Thyroidectomized injected	7.7	5.8	6.4	133	183	15
Hypophysectomized not injected	3.6	2.8	3.2	67	100	7
Hypophysectomized injected	9.1	8.4	8.7	181	272	6

* We have calculated the metabolism on the basis of body weight rather than surface area because of the difficulty in obtaining satisfactory figures for area. We have made careful measurements of skin area of a few animals and have arrived at values widely different from those obtained by Mitchell and Carman [24] or by use of Meeh's equation with Rubner's constant for the rat. Our measurements were made as follows: The animal was killed, two girths were marked around the trunk with ink, circumferences were measured at these marks as was length from the nose to the root of the tail. The skin was removed and stretched to these measurements on a sheet of paper, an outline of the skin was traced and the area measured with a planimeter. To this was added the area of the tail (length x circumference at middle) and the feet and ears (estimated). We hesitate to use the value for K derived from our measurements on account of the paucity of our data. However, temporarily assuming the correctness of our value for K we arrive at a basal rate for our normal rats which averages around 40 Cal. per square meter per hour which harmonizes well with Voit's [25] classical tabulation of Calories per square meter for animals of various sizes.

be well to point out again that in the work reported here the respiration chamber was maintained at a temperature of 28.5° – 29.5° C., that metabolism was measured for short periods, and that only those periods were accepted during which the animal was quiet. The above-mentioned workers used periods of three to seven hours and we do not find that they insisted on complete muscular rest on the part of their subjects. The group of unoperated animals receiving thyroid injections showed (as the mean of 15 observations)

a basal metabolism of 5.5 Cal. per kilogram per hour (maximum 6.3, minimum 5.2). Comparing the mean values for the two groups we find that the thyroid-injected animals average 15 per cent higher than the untreated normals. This stimulating effect of thyroid upon the basal metabolism has been observed many times since the pioneer work of Magnus-Levy (Literature in Grafe [10]).

From the data in the literature it seems that the administration of thyroid to normal animals causes only a rather moderate increase in metabolism over a very wide range of dosages. For example, Miyazaki and Abelin [8] feeding daily 111 mg. of desiccated thyroid to rats found approximately 20 to 25 per cent increase in metabolism; whereas Cramer and M'Call [11] with the massive dose of 0.5 gm. dry gland daily to rats, found increases no larger. Our minute dosage yielded an average increase of 15 per cent.

The Thyroidectomized Rat. As is shown in Table 1, the mean of 15 observations of basal metabolism of thyroidless rats receiving no thyroid injections is 3.5 Cal. per kilogram per hour (maximum 4.0, minimum 3.2), while in the thyroidectomized animals receiving thyroid injections the mean of 15 observations is 6.4 (maximum 7.7, minimum 5.8). From this it appears that the effect of thyroid injections is greater on the thyroidectomized animals than on the unoperated group. Thus, whereas thyroid injections increased the basal metabolism of the unoperated animal by 15 per cent, the same therapy applied to the thyroidectomized rats raised the metabolism by 83 per cent. The metabolism of the operated-injected group is even greater than that of the unoperated-injected animals (*i. e.*, mean values of 6.4 and 5.5 Cal. per hour respectively).

Reference to Table 2 shows that our thyroidless rats which received no replacement therapy maintained their subnormal metabolism for at least nine or ten weeks after operation (as long as the experiment was continued). This is not in agreement with the work of Cramer and M'Call [12] who report that the decreased metabolism after thyroidectomy in the rat is only temporary and that after three or four weeks the metabolic rate returns to normal. Such would presumably be the case if the thyroidectomy were incomplete and a fragment of the gland regenerated. That this may be the explanation of Cramer and M'Call's results is a possibility in view of their statement that at necropsy the absence of thyroid tissue was confirmed only by naked eye examination. As shown in

TABLE 2

Basal Metabolism of Thyroidectomized Animals

Designation of animal	Age at operation	Period of no thyroid treatment			Period of thyroid treatment		
		Age at metabolic test	No. of days between operation and metabolic test	Basal metabolism	Age at metabolic test	No. of days between beginning (or stopping) thyr. injections and metab. test	Basal metabolism
	Days	Days		Cal. Kg. hr.	Days		Cal. Kg. hr.
BH 325.....	42	111	69	3.60			
		114	72	3.47			
					122	2	4.47
					128	8	5.45
					135	15	5.67
					141	21	5.75
W 335.....	40	65	25	3.72			
		67	27	3.67			
		70	30	3.66			
					120	5	5.44
					124	9	6.49
W 332.....	40	99	59	3.50			
					131	16	5.26
BH 330.....	42	80	38	3.80			
		88	46	3.74			
BH 318.....	48	97	49	3.35			
		103	55	3.50			
		Period of thyroid treatment*			Period of no thyroid treatment		
GH 336.....	40	67	27	6.78			
		70	30	6.61			
					131	16	3.97
B 328.....	42	80	38	5.97			
		88	46	6.04			
					129	10	3.72
BH 333.....	40	99	59	5.70			
					120	7	4.86
					123	10	4.10
					125	12	4.02
GH 319.....	48	97	49	6.51			
		103	55	6.30			
W 329.....	42	111	69	6.27			

* Daily thyroid injections were begun immediately after operation.

Table 2 (animals 328, 333, and 336), when the daily thyroid injection of the operated animal was stopped eleven weeks after operation the basal metabolism soon fell from the high level which had been maintained by the thyroid therapy and reached cretinoid levels within two weeks after the injections were stopped, or thirteen weeks after removal of the thyroids. Thus over a period of from ten to thirteen weeks after thyroidectomy there was no indication of the "compensatory mechanism" postulated by Cramer and M'Call in either the treated or the untreated group.

The Hypophysectomized Rat. Our observations on this group, though few, are concordant and a much larger series probably would not significantly change the conclusions that can be drawn from the observations recorded here (Table 1). Seven duplicate determinations of basal metabolism of hypophysectomized rats gave results ranging from 2.8 to 3.6 Cal. per kilo per hour, the mean being 3.2 * (Foster and Smith [13]). To compare with these we have six observations on two hypophysectomized animals receiving daily thyroid injections which showed the remarkably high level of 8.7 Cal. per kilo per hour (max. 9.1, min. 8.4). (These measurements like all those reported here were made while the animal was at rest.) On the basis of mean values, the thyroid injections increased the basal metabolism of the hypophysectomized animal by 170 per cent. As compared with the untreated, normal controls, the increase is 81 per cent. The lowest figure for basal rate in this group is considerably higher than the maximum value in any of the other groups.

Effect upon the Specific Dynamic Action of Amino Acids and Glucose

In Figs. 1 and 2 are shown results typical of the specific dynamic action experiments. They are representative of the findings as a whole. In the normal rat following the intraperitoneal injection of glucose or glycocoll there is a prompt rise (within 30 minutes) above the basal rate. This persists for one to two hours and then begins to decrease, disappearing within about three to four hours after the injection. The average of nineteen experiments shows an increase of 16 per cent above the basal for a period of three hours. Similar injections of normal saline do not affect the metabolic rate.

* This very low rate per kilogram in the hypophysectomized animal is not due to large deposits of inert fat. Hypophysectomy does not induce obesity (Smith[4]).

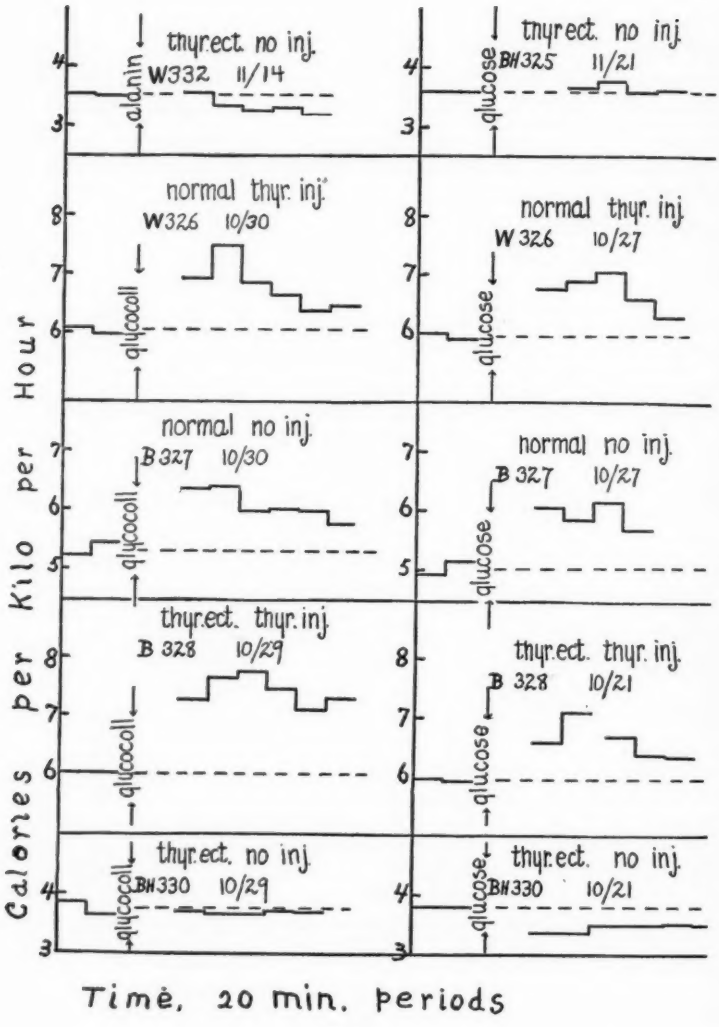

FIG. 1

Metabolism, in 20 minute periods, before and after intraperitoneal injection of amino acids or glucose. The broken line represents the basal rats.

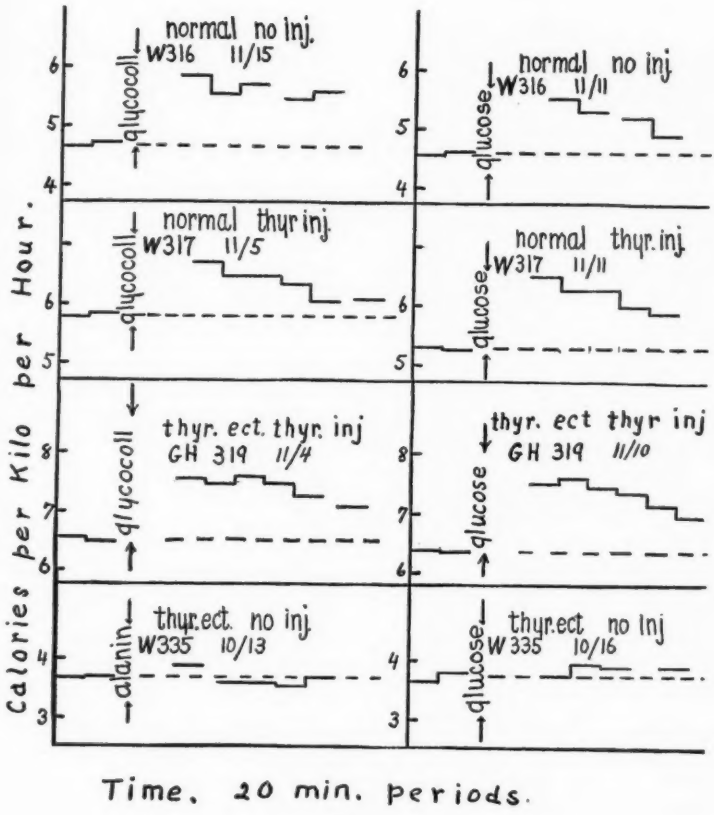

FIG. 2

Metabolism, as in Fig. 1, before and after amino acid and glucose injections.

It will be seen that in animals thyroidectomized some weeks previously the specific dynamic action of glucose or amino acid is uniformly absent, a finding which agrees with those of Baumann and Hunt [14] in thyroidectomized rabbits. In the parallel series of thyroidectomized animals receiving daily injections of thyroid substance, the specific dynamic effect was in full play as was also the case with the unoperated animals receiving thyroid injections.

After several weeks the treatment of the two groups of thyroidless animals was reversed, *i. e.*, the thyroidectomized animals which had been receiving thyroid injections now received none and *vice versa*. Our metabolism data after reversal of the thyroid therapy, though not sufficiently abundant to warrant much discussion, seem to indicate that the animals which had been receiving replacement therapy lost the specific dynamic response within ten days after the thyroid injections were stopped. This is much sooner than one would expect in view of the findings of Baumann and Hunt [14] on rabbits where the specific dynamic action of glucose did not completely disappear until sixty-five days after thyroidectomy.

Animals thyroidectomized for a sufficient length of time to have the specific dynamic response abolished developed the characteristic response to glycocoll injection within fifteen days after thyroid treatments were begun.

As was previously reported (Foster and Smith [13]) no specific dynamic action was observed with the untreated hypophysectomized animals. For the thyroid-injected, hypophysectomized rats we have no satisfactory specific dynamic action experiments. The animals were too restless after the administration of the glycocoll to permit taking accurately the metabolic rate. This point is of interest in connection with the extremely high basal metabolism found in this group of animals (see preceding section). It was possible, by exercising considerable patience, to obtain basal periods during which these animals were quiet, but in the three hours following the injection of glycocoll it was not possible to obtain a single twenty-minute period uncomplicated by movement of the animal, whereas the other animals would often sleep quietly for nearly the whole time.

Effects upon Growth

The Normal Unoperated Rat. Reference to Table 3 shows that our thyroid dosage did not alter in any marked degree either the general body weight or the length of normal animals, as compared with their untreated littermate controls. The variations exhibited are clearly within the normal limits. Growth inhibition from thyroid administration has been reported by Cameron and Carmichael,[1, 2] and Gudernatch [16]; while no influence or a slight increase in the rate of growth is reported by Herring,[17, 18] Hoskins [19] and Schäfer.[20] That this difference in the effects upon growth is due to the amount of thyroid administered has been clearly shown by the work of Herring [18] Hewitt [26] and Cameron and Carmichael.[1] It appears that our dosage is too small to influence body weight or skeletal growth. An examination of the adrenal weights of our thyroid-injected normal animals shows in but one case any increase over the normal. In this case the increase in weight is not great enough to appear of significance. These results are not in harmony with the findings of other investigators; the adrenal hypertrophy, induced by thyroid feeding, reported by R. G. Hoskins [22] having been uniformly confirmed. This failure of our thyroid dosage to cause any alteration in the rate of general body growth or in the weights of the adrenals is here emphasized for it shows the minuteness of our dosage. Nevertheless, this small dose when given to the thyroidless rat exerted a profound effect as will be shown in the next section.

The Thyroidectomized Rat. Although the first successful replacement therapy was achieved in operative myxedema or endemic cretinism, experimental investigators appear not to have attempted a replacement therapy in the thyroidectomized animals. The effect of thyroidectomy, however, has been thoroughly studied by a number of investigators who have reported, among other effects, a retardation in the rate of general body growth and a diminution in the weight of adrenals. Our thyroidectomized animals, of which we had quite a large series, showed these characteristic effects. Since our data upon this point are harmonious with that given by other investigators it seems unnecessary to present it here. We have pointed out above that our small thyroid dosage failed to elicit any appreciable response in the unoperated animals. In contrast to this is the striking response elicited in the thyroidectomized

TABLE 3

Table Giving the Data for Animals not Represented in Figs. 3 and 4

Designation and Type; Female rats	Operation			Treatment begun *				Experiment terminated			Number days of treatment	Change during treatment in		Absolute weight of		Relative percentage weight	
	Age, days	Weight, gm.	Length, mm.	Substance injected	Age	Weight	Length	Age	Weight	Length		Weight	Length	Adrenals	Ovaries	Adrenals	Ovaries
W 643 Hypophysectomized	43	114	286	Thyroid	53	103	289	98	108	306	45	5	17	0.0091	0.0120	.38	.45
W 644 Hypophysectomized	43	110	284	Thyroid	53	98	288	98	101	303	45	3	15	0.0081	0.0096	.37	.38
B 646 Hypophysectomized	43	132	288	Thyroid	53	109	290	98	110	305	45	1	15	0.0093	0.0160	.38	.59
B 645 Normal	43	122	296	None	53	148	316	98	206	364	45	58	48	0.0453	0.0508	1.00	1.00
B 647 Normal	43	110	273	None	53	129	296	98	185	356	45	56	60	0.0483	0.0531		
W 159 Thyroidectomized	71	146	340	None	75	148	340	182	185	351	107	37	11	0.0240	0.0387	.56	.70
GH 160 Thyroidectomized	71	150	340	None	75	148	340	182	170	350	107	22	10	0.0202	0.0377	.50	.77
BH 162 Thyroidectomized	71	142	334	Thyroid	75	142	334	182	204	382	107	62	48	0.0501	0.0603	1.05	1.02
GH 161 Normal	71	149	339	Thyroid	75	151	339	182	237	395	107	86	56	0.0522	0.0686	.94	1.00
GH 158 Normal	71	182	354	None	75	179	354	182	220	396	107	41	42	0.0515	0.0639	1.00	1.00
BH 318 Thyroidectomized	48	104	291	None	52	114	293	124	151	314	72	37	21	0.0227	0.0399	.68	1.13
GH 319 Thyroidectomized	48	103	283	Thyroid	52	109	285	124	195	355	72	86	70	0.0541	0.0474	1.36	1.04
W 317 Normal	48	101	290	Thyroid	52	109	291	124	201	374	72	92	83	0.0606	0.0623	1.36	1.32
W 316 Normal	48	101	292	None	52	111	293	124	212	378	72	101	85	0.0470	0.0496	1.00	1.00
W 151 Thyroidectomized	83	182	349	Thyroid	87	178	349	194	253	391	107	75	42	0.0583	0.0593	1.12	1.02
W 153 Normal	83	173	354	Thyroid	87	175	354	194	222	395	107	47	41	0.0496	0.0654	1.08	1.31
BH 154 Normal	83	174	353	None	87	175	353	194	217	394	107	42	41	0.0447	0.0489	1.00	1.00

* For comparison the weight and age of the animals receiving no treatment is also given in this column.

animal by this same dosage. It brought about a normal growth rate in these animals which prior to treatment were growing slowly or not at all. It thus had a pronounced effect upon growth both as regards body weight and total length (Table 3, Fig. 3). The adrenals also, at necropsy, were of normal size and structure in these treated animals, thus showing the restorative effects of this treatment upon these glands. It seemed to us a striking example of the

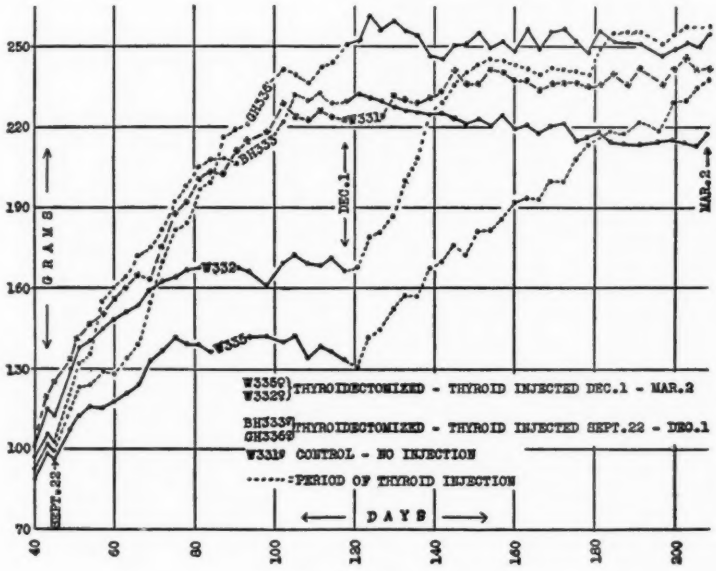

FIG. 3

Curves showing body weight of four thyroidectomized rats and one control, all littermates. Two of the thyroidectomized animals (BH333, GH336) received thyroid injections during only the first half of the period, the other two (W332, W335) during only the last half.

utilization of a secretory product when a physiologic deficit exists. That the normal animal was not affected by this dosage shows the stability of the balance which exists among the endocrine glands and the capacity of the normal animal to withstand an unusual amount of thyroid secretion.

The Hypophysectomized Rat. In five hypophysectomized rats (Table 3, Fig. 4) we have injected over a considerable period of time the same thyroid dosage in proportion to body weight given to

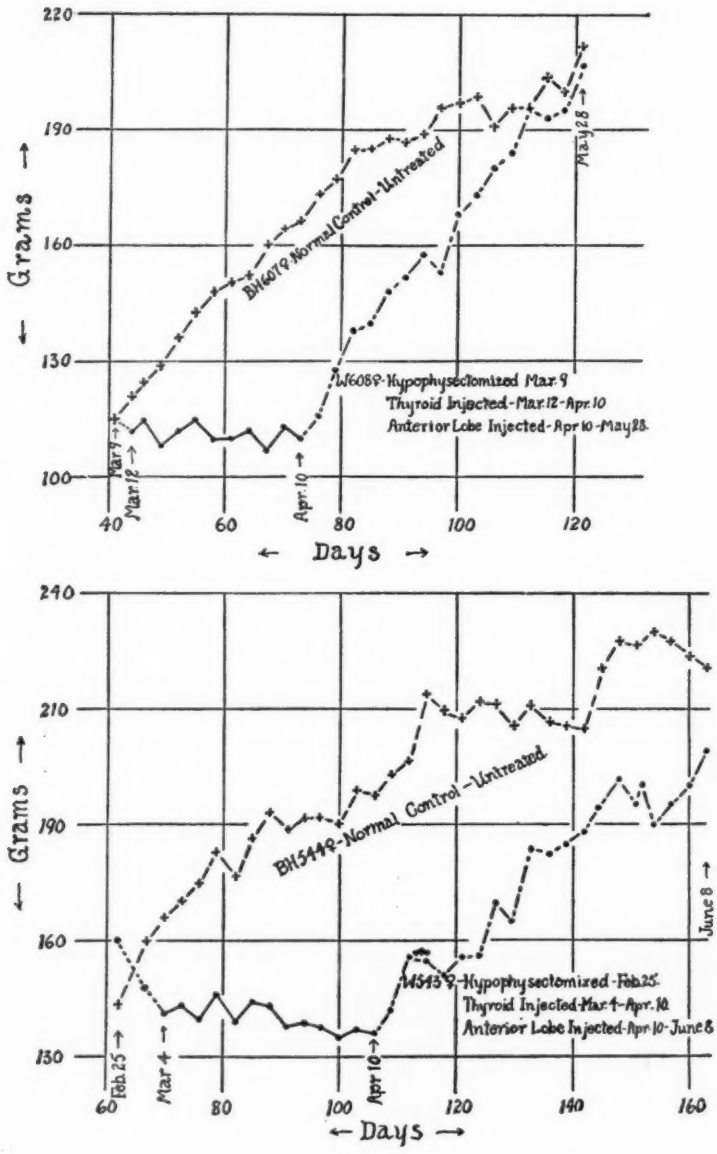

FIG. 4

Curves showing body weights of two hypophysectomized rats and the littermate controls. The former received thyroid injections during the first part of the period, followed by anterior pituitary injections. The controls received no treatment.

the normal and to the thyroidectomized animal. This treatment neither stimulated growth in animals whose growth had been stopped by pituitary ablation nor did it repair the endocrine organs and the genital system which atrophy as a result of hypophysectomy (Smith [4]).

That the failure of the thyroid treatment to stimulate general body growth or growth of the adrenals and the genital system is not due to any incapacity of these animals to respond to treatment is shown by the fact that daily anterior pituitary transplants stimulate their general body growth and have a marked restorative effect upon their atrophied adrenals, thyroids and genital system (Smith [4]). Daily intraperitoneal injections of a fresh bovine anterior pituitary suspension also stimulates their general body growth although it does not restore the atrophied endocrine organs or genital system. In order to contrast the absence of any growth stimulation from thyroid administration with the growth stimulation given by the anterior pituitary we present in Fig. 4 the growth curves of animals which were, for a period, injected with thyroid, this being followed by a period in which injections of a bovine anterior pituitary suspension were given.

The failure of thyroid administration to induce growth in these pituitaryless animals is in accord with results obtained in clinical cases of pituitary dwarfs, in which thyroid treatment is ineffective. In the absence of the pituitary secretion the thyroid cannot induce growth.

Discussion

We have shown that injections of thyroid extract in minute doses, given in proportion to body weight, give, as regards basal metabolism, growth, and organ weights, very different effects in the different groups of animals studied.

A thyroid dosage which does not appreciably alter the growth rate or the adrenal weights of unoperated controls induces a normal increase in body weight, in total length and in the weights of the adrenals in rats stunted by thyroidectomy. The thyroid-injected, thyroidectomized animals thus markedly exceeded in body weight and in the weight of their adrenals their uninjected, thyroidless, littermate controls. We have no explanation which satisfies us for this difference in the response to thyroid injection of the thyroidec-

tomized as compared with the normal rat. An avascularity and a smaller size of the thyroids in thyroid-treated normal rats (Cameron and Sedziak [15]) may form a part of the mechanism by which the amount of the thyroid hormone may be controlled as has been suggested by these investigators. That it does not form the entire mechanism for such a control appears from the determinations of the basal metabolism in the thyroidectomized and the hypophysectomized rat receiving thyroid treatment. Although the amount of thyroid administered was identical, in proportion to body weight, yet the rise in the metabolic rate of the thyroidless was considerably greater than it was in the normal rat, and the response of the hypophysectomized animal was even more profoundly increased. This greater rise of the thyroidless and hypophysectomized animal as compared with the normal, cannot be referred to any compensatory inactivity of the thyroids in the operated animals for in one the thyroids were absent and in the other they were atrophied.

Our work also clearly shows that in the absence of the hypophysis growth cannot be brought about by thyroid treatment. It would seem that the growth stimulation induced by thyroid administration in the thyroid dwarf is due to a stimulation in the secretory activity of the hypophysis. This conclusion is in harmony with the findings of Trautman who interpreted the hypophyseal changes following thyroidectomy as degenerative in nature and with those of Livingston [23] who found that thyroid feeding prevented these changes. It is supported also by the work of Flower and Evans who found that injection of a suspension of bovine hypophysis induced growth in the thyroidless rat, and by the fact that injection of this bovine pituitary suspension or pituitary transplants induced growth in the hypophysectomized rat (Smith [4]).

Our experiments, in common with those of many other investigators, show the stimulating effect of thyroid administration upon the basal metabolism of the normal animal. It is of interest to compare the effect upon metabolism with the size of the dose of the thyroid given. Miyazaki and Abelin [8] fed from 75 to 110 mg. of desiccated thyroid daily to rats of approximately 150 gm. weight and recorded increases in basal metabolism of from 15 to 25 per cent. From the data reported by Cramer and M'Call [11] it is difficult to make definite recalculations, but in most cases the increase in metabolism induced by the massive dose of 500 mg. of dry gland daily to a 150

gm. rat is less than 25 per cent. Our dosage prepared and administered as described under "Methods" would correspond to about 8 mg. of dry gland substance for a 150 gm. rat if we assume fresh sheep thyroid to contain 75 per cent water. This dosage resulted in an average increase of 15 per cent above the normal basal level. In the reports of the above-named workers we have no assurance that the whole dose of thyroid was in each case consumed and a strict comparison of their dosages with ours is probably not possible. However, it seems that large doses have relatively less effect than do small and that the normal organism is in some manner well "buffered" against excessive amounts of thyroid secretion. Whatever this hypothetical "buffering mechanism" may be, it appears to be less effective in the thyroidectomized and far less effective in the hypophysectomized animal, as can be shown by a comparison of the actual increase in Cal. per Kg. per hour of the treated over the untreated animal of each type. Thus, in the unoperated animal the mean increase induced by thyroid injections was 5.5 less 4.8 or 0.7 Cal. per Kg. per hour; in the thyroidectomized group the increase was 6.4 less 3.5 or 2.9 Cal. per Kg. per hour and in the hypophysectomized animal 8.7 less 3.2 or 5.5 Cal. per Kg. per hour. That is, the *increase* in basal heat production caused by thyroid injections was 4.1 times greater in the thyroidectomized and 7.9 times greater in the hypophysectomized than in the unoperated animal.

Our experiments showing the absence of specific dynamic action of amino acids and glucose in thyroidectomy confirm the work of Baumann and Hunt.[14] They do not, however, lead to any explanation of the nature or cause of specific dynamic action. It is not at all likely that there is a qualitative difference in the manner in which these substances are metabolized by thyroidless animals. It seems more probable that it is a matter of reaction velocities. It is planned to compare the rates of absorption and the completeness of utilization of glucose and amino acids by normal and thyroidectomized animals.

Summary

Minute doses of a saline extract (suspension) of fresh sheep thyroids were injected daily into normal, thyroidectomized or hypophysectomized rats. The dosage was given in proportion to body weight, 0.02 cc. being given for each 25 gm. body weight.

Normal rats gave no growth or marked adrenal response to these injections.

Thyroidectomized rats, on the other hand, gave a pronounced growth and adrenal response. Their rates of growth and adrenal weights consequently greatly exceeded those of their untreated thyroidectomized littermates.

Rats which had been stunted by hypophysectomy showed neither growth response to the injections nor restoration of their atrophied adrenals, thyroids, or genital systems. This failure of the thyroid injections is not due to any incapacity of these animals to respond to treatment, for pituitary transplants cause them to grow and have a marked restorative effect upon their atrophied endocrine and genital systems. In the absence of the anterior pituitary secretion, the thyroid cannot stimulate growth.

Thyroid injections have much greater effect upon the basal metabolism of thyroidectomized and still greater effect upon that of hypophysectomized rats than upon that of unoperated animals.

In agreement with Baumann and Hunt,[14] the specific dynamic action of glucose, glycocoll and alanin is absent in thyroidectomized rats six weeks or more after operation. In thyroidless rats receiving replacement therapy, specific dynamic action is in full play.

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INDEX OF SUBJECTS

INDEX OF SUBJECTS

A

Addison's disease. — A report of two cases of essential adrenal insufficiency (. . .) (*Medlar*) - 135

Adenocarcinoma. — . . . of the uterus in a rabbit (*Rusk and Epstein*) - 235

Adenosis. — Diffuse . . . of vagina: a very rare disease (*Plaut*) - - - - 581*

Adrenal cell emboli. — The organization of experimental . . . in the lungs (*Simonds*) - 13

Adrenal insufficiency. — A report of two cases of essential . . . (Addison's disease (*Medlar*) - 135

Anemia. — Osteosclerotic . . . secondary to epidermoid carcinoma (*Rusk and Miles*) - 289

Anemia. — The pathology of the bone marrow in pernicious . . . (*Peabody*) - 179

Antigens. — A comparative study of basic beef heart . . . in the Wassermann test (*Albray and Famulener*) - - - - - - - - - - - - - - - - 539*

Aorta. — Coarctation of . . . (adult type) with complete obliteration of descending arch (*Abbott*) - 572*

Aorta. — Right-sided . . . (persistence of the right aortic arch) (*Arkin*) 572*

Aortitis. — The heart in syphilitic . . . (*Clawson*) - - - - - - - - - - - - 575*

Aortitis. — The involvement of the aortic valve in syphilitic . . . (*Saphir and Scott*) - 527

Aortitis. — The involvement of the aortic valve in syphilitic . . . (*Saphir and Scott*) - 574*

Argyria. — A contribution to the pathology of generalized . . . with a discussion of the fate of silver in the human body (*Gettler, Rhoads and Weiss*) - 631

Arteriosclerosis. — Pulmonary . . . associated with primary carcinoma of the lung (*Boyd*) - 574*

Attenuation. — Studies of . . . and of toxic production of the diphtheria bacillus (*Wheeler*) - 540*

B

Bacteria. — The incidence of various species of . . . in specimens of spinal fluid from cases of meningitis (*Gilbert and Coleman*) - - - - - 542*

Bacteriophage. — The demonstration of . . . in old stock cultures (*Kline*) - 561*

Bacteriophage. — The particulate nature of . . . (*Bronfenbrenner*) - - 561*

Bacteriophage. — The study of intimate mechanism of the lysis of bacteria by . . . (*Bronfenbrenner, Muckenfuss and Hetler*) - - - - - - 562*

* Abstract of paper presented at the meeting of the Association of Pathologists and Bacteriologists held at Rochester, N. Y., April 15 and 16, 1927.

Blastomycosis. — Pulmonary . . .; its similarity to tuberculosis. Report of two cases (*Medlar*) - 305

Blastomycosis. — Pulmonary . . .; its similarity to tuberculosis. Report of two cases (*Medlar*) - 567*

Blastomycosis. — The reticulum of the lung. V. Its similarity in . . . to that in tuberculosis (*Miller*) - 315

Blood pressure readings. — A bloodless method for taking repeated . . . in laboratory animals (*McGregor*) - - - - - - - - - - - - - - - - - - - 576*

Bone marrow. — The pathology of the . . . in pernicious anemia (*Peabody*) - 179

C

Carcinoma. — A case of hypoglycemia, probably produced by a . . . of the islands of Langerhans (*Robertson*) - - - - - - - - - - - - - - - - 571*

Carcinoma. — Diffuse lymphoma of mesentery associated with . . . of colon (*Schultz*) - 549*

Carcinoma. — Osteosclerotic anemia secondary to epidermoid . . . (*Rusk and Miles*) - 289

Carcinoma. — Pulmonary arteriosclerosis associated with primary . . . of the lung (*Boyd*) - 574*

Casts. — The histogenesis of urinary . . . (*Jackson*) - - - - - - - - - - - 285

Cathode rays. — The effect of high voltage . . . on living tissue; an experimental study (*Jacobson and Waddell*) - - - - - - - - - - - - - - - 560*

Coarctation. — . . . of aorta (adult type) with complete obliteration of descending arch (*Abbott*) - 572*

Coccidioidal meningitis. — . . . (*Rusk and Buck*) - - - - - - - - - - - - 568*

Colon-typhoid group. — Siphonic fermentation tube for the more rapid isolation of the . . . of organisms (*Jones*) - - - - - - - - - - - - - - 542*

D

Dermal testing. — . . . as an aid to diagnosis of intestinal parasitic infestation (*Brunner*) - 540*

Dermoid. — Malignant mediastinal . . . with meningeal metastasis (*Jacobs*) - 556*

Dietary means. — Experimental gangrene produced by . . . (*Smith and Bogin*) - 67

Differential. — Transplantation and individuality . . . in strains of inbred rats (*Loeb and King*) - 143

Differentials. — Transplantation and individuality . . . in inbred families of guinea pigs (*Loeb and Wright*) - - - - - - - - - - - - - - - - - 251

Diphtheria bacillus. — Studies of attenuation and of toxic production of the . . . (*Wheeler*) - 540*

Dust cell. — Studies on endothelial reactions. X. On the origin of the pulmonary " . . ." (*Foot*) - 413

E

Embolism. — Report of seventy-three cases of pulmonary . . . (*McCartney*) - 572*

Encephalitis. — Nuclear changes of ganglion cells in experimental herpetic . . . (*Goodpasture*) - 395

Endocarditis. — Vegetative . . . due to the meningococcus with a case report (*Rhoads*) - 623

Endometriosis. — Metastatic or embolic . . ., due to the menstrual dissemination of endometrial tissue into the venous circulation (*Sampson*) - 93

Endothelial reactions. — Studies on . . . X. On the origin of the pulmonary "dust cell" (*Foot*) - 413

Erysipelas streptococcus toxin. — Immunization of horses to . . . (*Anderson and Leonard*) - 541*

F

Fetus. — A quantitative study of the hypophysis of the human anencephalic . . . (*Covell*) - 17

Fibrosarcoma. — Tumor and foreign body giant cells in a . . . of the uterus (*Mallory and Stewart*) - 85

Filtration. — Some points on the mechanism of . . . by the spleen (*Robinson*) - 568*

G

Ganglion cells. — Nuclear changes of . . . in experimental herpetic encephalitis (*Goodpasture*) - 395

Ganglioneuroma. — The transformation of a malignant paravertebral sympathicoblastoma into a benign . . . (*Cushing and Wolbach*) - - 203

Gangrene. — Experimental . . . produced by dietary means (*Smith and Bogin*) - 67

Giant cells. — Tumor and foreign body . . . in a fibrosarcoma of the uterus (*Mallory and Stewart*) - 85

Glomerulonephritis. — Spontaneous intracapillary . . . in the rabbit (*Mallory and Parker*) - 91

Glomerulus. — The state of the . . . in experimental hypertrophy of the kidneys of rabbits (*Saphir*) - 329

Goat serum. — The absorption of the toxic substance of normal . . . by guinea pig tissue (*Aronson*) - 539*

Grumbach. — Experiments of two years on the relation of Hodgkin's disease and the organism isolated by . . . (*Fox*) - - - - - - - - - - - 544*

Guinea pig. — Syngenesiotransplantation in the . . . (*Loeb*) - - - - - - 29

Guinea pigs. — The effect of age of the host on the fate of transplants of thyroid glands in . . . (*Tureen*) - - - - - - - - - - - - - - - - - - - 501

Guinea pigs. — Transplantation and individuality differentials in inbred families of . . . (*Loeb and Wright*) - - - - - - - - - - - - - - - - - 251

Guinea pig tissue. — The absorption of the toxic substance of normal goat serum by . . . (*Aronson*) - 539*

H

Heart. — A congenital anomaly of the . . .: truncus arteriosus communis (*Zimmerman*) - 617

Heart. — The . . . in syphilitic aortitis (*Clawson*) - - - - - - - - - - - 575*

Heart. — Malformations of the . . . including two cases with common atrioventricular canal and septum defects and one with defect of the atrial septum (cor triloculare biventriculosum) (*Gunn and Dieckmann*) - 595

Hearts. — Three specimens of . . . showing congenital lesions (*Crawford and Weiss*) - 572*

Hepatoma. — A case of primary mesenchymal . . . with necropsy (*Foot*) 653

Herpetic encephalitis. — Nuclear changes of ganglion cells in experimental . . . (*Goodpasture*) - 395

Hodgkin's disease. — Experiments of two years on the relation of . . . and the organism isolated by Grumbach (*Fox*) - - - - - - - - - - - - - 544*

Hodgkin's disease. — Intra-vital staining and phagocytosis in . . ., leukemia and sarcoma (*Fox*) - 546*

Hodgkin's disease. — The neoplastic relationship of . . ., aleukemic and leukemic lymphoblastomas and mycosis fungoides (*Warthin*) - 551*

Hog cholera. — The bacteriology of the blood of swine with particular reference to the virus of . . . (*Lewis*) - - - - - - - - - - - - - - - - 561*

Hyaline degeneration. — . . . of the islands of Langerhans in non-diabetics (*Wright*) - 461

Hyperplasia. — Malignant lymph follicle . . . of spleen and lymph nodes (*Baehr and Rosenthal*) - 550*

Hypersensitiveness. — Local . . . (*Dienes*) - - - - - - - - - - - - - - - - 539*

Hypertension. — A method of producing experimental chronic . . . in the rabbit (*Pederson*) - 577*

Hypertension. — Analysis of four hundred cases of primary . . . (*Bell*) 578*

Hypertrophy. — The state of the glomerulus in experimental . . . of the kidneys of rabbits (*Saphir*) - 329

Hypoglycemia. — A case of . . . , probably produced by a carcinoma of the islands of Langerhans (*Robertson*) - - - - - - - - - - - - - - - - 571*

Hypophysis. — A quantitative study of the . . . of the human anencephalic fetus (*Covell*) - 17

I

Immunization. — Active . . . against experimental peritonitis (*Steinberg and Goldblatt*) - 541*

Immunization. — . . . of horses to erysipelas streptococcus toxin (*Anderson and Leonard*) - 541*

Intra-vital staining. — . . . and phagocytosis in Hodgkin's disease, leukemia and sarcoma (*Fox*) - 546*

Islands of Langerhans. — A case of hypoglycemia, probably produced by a carcinoma of the . . . (*Robertson*) - - - - - - - - - - - - - - - 571*

Islands of Langerhans. — Hyaline degeneration of the . . . in non-diabetics (*Wright*) - 461

Islands of Langerhans. — Studies on the . . . in human pancreas. I. The relation of the islands to the surrounding structures (*Otani*) - - - 1

Islands of Langerhans. — Studies on the . . . in the human pancreas. II. Significance of variations in structure (*Otani*) - - - - - - - - - - 123

K

Kaposi. — Multiple hemorrhagic sarcoma of . . . (*Meyers and Jacobson*) - 321

Kidneys. — The etiologic study of the pathology of eighteen congenital polycystic . . . (*Davis*) - 570*

L

Leukemia. — Acute . . . with extra medullary myeloid centers (*Marshall and Woodward*) - 547*

Leukemia. — Generalized reticular-cell sarcoma of lymph nodes, associated with lymphatic . . . (*Richter*) - - - - - - - - - - - - - - - - - 547*

Leukemia. — Intra-vital staining and phagocytosis in Hodgkin's disease, . . . and sarcoma (*Fox*) - 546*

Lipoid solvents. — Local and systemic changes induced by . . . in animals fed on diets varying in vitamin content (*Jorstad and Johnston*) 489

Liver. — Histological and chemical observations upon the origin of the polycystic . . . (*Scott*) - 570*

Lung. — Pulmonary arteriosclerosis associated with primary carcinoma of the . . . (*Boyd*) - 574*

Lung. — The reticulum of the . . . IV. Its presence in the reparative process of the tuberculous lesion with and without caseation (*Miller*) - 217

Lung. — The reticulum of the . . . V. Its similarity in blastomycosis to that in tuberculosis (*Miller*) - 315

Lungs. — The organization of experimental adrenal cell emboli in the . . . (*Simonds*) - 13

Lymph follicle hyperplasia. — Malignant . . . of spleen and lymph nodes (*Baehr and Rosenthal*) - 550*

Lymph nodes. — Malignant lymph follicle hyperplasia of spleen and . . . (*Baehr and Rosenthal*) - 550*

Lymphadenopathies. — Relation of polynuclear neutrophiles and their reaction to X-ray, to certain . . . (*Fox*) - - - - - - - - - - - - - - - 545*

Lymphatic system. — The first annual report of the registry of tumors of the . . . (*Callender and Coupal*) - - - - - - - - - - - - - - - - - - - 543*

Lymphoblastomas. — The neoplastic relationship of Hodgkin's disease, aleukemic and leukemic . . . and mycosis fungoides (*Warthin*) - - 551*

Lymphoma. — Diffuse . . . of mesentery associated with carcinoma of colon (*Schultz*) - 549*

Lysis. — The study of intimate mechanism of the . . . of bacteria by bacteriophage (*Bronfenbrenner, Muckenfuss and Heller*) - - - - - - 562*

M

Meningeal metastasis. — Malignant mediastinal dermoid with . . . (*Jacobs*) - 556*

Meningitis. — Coccidioidal . . . (*Rusk and Buck*) - - - - - - - - - - - - 568*

Meningitis. — The incidence of various species of bacteria in specimens of spinal fluid from cases of . . . (*Gilbert and Coleman*) - - - - - - 542*

Meningococcus. — Vegetative endocarditis due to the . . . with a case report (*Rhoads*) - 623

Menstruating. — . . . umbilical tumors (*Weller*) - - - - - - - - - - - - 553*

Mitochondria. — Studies on . . . II. The occurrence of . . . -rich and . . . -poor cells in the thyroid gland of man and animals (*Seecof*) - 365

Molluscum contagiosum. — A cytologic study of . . . (*Goodpasture and King*) - 385

Mycosis fungoides. — The neoplastic relationship of Hodgkin's disease, aleukemic and leukemic lymphoblastomas and . . . (*Warthin*) - - 551*

Myocardium. — Sarcosporidial infection of the . . . in man (*Lambert*) 663

N

Nerves. — Pathologic changes in the . . . of the stomach wall in cases of chronic gastric ulcer (*Okkels*) - - - - - - - - - - - - - - - - - - - 75

Nervous system. — The encapsulated tumors of the . . . (Meningeal fibroblastomas, perineurial fibroblastomas, and neurofibromas of von Recklinghausen) (*Penfield*) - - - - - - - - - - - - - - - - - - - 557*

Neutrophiles. — Relation of polynuclear . . . and their reaction to X-ray, to certain lymphadenopathies (*Fox*) - - - - - - - - - - - - - 545*

O

Ovary. — The sympathicotropic cells of the . . . and testis (*Brannan*) 343

P

Pancreas. — Studies on the islands of Langerhans in human . . . I. The relation of the islands to the surrounding structures (*Otani*) - - 1

Pancreas. — Studies on the islands of Langerhans in the human . . . II. Significance of variations in structure (*Otani*) - - - - - - - - - 123

Parasitic infestation. — Dermal testing as an aid to diagnosis of intestinal . . . (*Brunner*) - 540*

Periarteritis obsoleta nodosa. — . . . A study of the histologically healed end-stage (*Arkin*) - 576*

Peritonitis. — Active immunization against experimental . . . (*Steinberg and Goldblatt*) - 541*

Pernicious. — The pathology of the bone marrow in . . . anemia (*Peabody*) - 179

Phagocyte. — The origin of the alveolar . . . studied in paraffin sections of tissue stained supravitally with neutral red (*Gardner and Smith*) 445

Phagocyte. — The origin of the alveolar . . . studied in paraffin sections of tissue stained supravitally with neutral red (*Gardner and Smith*) 579*

Phagocytosis. — Intra-vital staining and . . . in Hodgkin's disease, leukemia and sarcoma (*Fox*) - 546*

Polycystic kidneys. — The etiologic study of the pathology of eighteen congenital . . . (*Davis*) - 570*

Polycystic livers. — Histological and chemical observations upon the origin of the . . . (*Scott*) - 570*

Protein. — Studies on the absorption of unaltered . . . (*Walzer*) - - - 539*

Pulmonary embolism. — Report of seventy-three cases of . . . (*McCartney*) - 572*

Pyorrhea alveolaris. — . . . : The rôle of certain microörganisms found in the lesions (*Fisher*) - 169

R

Rabbit. — A method of producing experimental chronic hypertension in the . . . (*Pederson*) - 577*

Rabbit. — Spontaneous intracapillary glomerulonephritis in the . . . (*Mallory and Parker*) - 91

Rat. — Syngenesiotransplantation in the . . . (*Loeb*) - - - - - - - - - - 45

Rats. — A comparison in normal, thyroidectomized and hypophysectomized . . . of the effects upon metabolism and growth resulting from daily injections of small amounts of thyroid extract (*Smith, Greenwood and Foster*) - 669

Rats. — Transplantation and individuality differential in strains of inbred . . . (*Loeb and King*) - 143

Registry of tumors. — The first annual report of the . . . of the lymphatic system (*Callender and Coupal*) - - - - - - - - - - - - - - - - - 543*

Reticulin fibrils. — On the origin of . . . (*Foot*) - - - - - - - - - - - - - 401

Reticulum. — . . . (*Mallory and Parker*) - - - - - - - - - - - - - - - - - 515

Reticulum. — . . . (*Mallory and Parker*) - - - - - - - - - - - - - - - - - 553*

Reticulum. — The . . . of the lung. IV. Its presence in the reparative process of the tuberculous lesion with and without caseation (*Miller*) - 217

Reticulum. — The . . . of the lung. V. Its similarity in blastomycosis to that in tuberculosis (*Miller*) - 315

Rheumatic fever. — Studies in the pathology of . . . Two cases presenting unusual cardiovascular lesions (*Pappenheimer and Von Glahn*) - 583

S

Sarcoma. — Generalized reticular-cell . . . of lymph nodes, associated with lymphatic leukemia (*Richter*) - - - - - - - - - - - - - - - - - 547*

Sarcoma. — Intra-vital staining and phagocytosis in Hodgkin's disease, leukemia and . . . (*Fox*) - 546*

Sarcoma. — Multiple hemorrhagic . . . of Kaposi (*Meyers and Jacobson*) - 321

Sarcosporidial infection. — . . . of the myocardium in man (*Lambert*) 663

Spinal fluid. — The incidence of various species of bacteria in specimens of . . . from cases of meningitis (*Gilbert and Coleman*) - - - - - - - 542*

Spirochetosis. — Pulmonary . . . (*Smith and Rusk*) - - - - - - - - - - - 225

Spleen. — The finer vascular channels of the . . . (*MacNeal, Otani and Patterson*) - 111

Spleen. — Malignant lymph follicle hyperplasia of . . . and lymph nodes (*Baehr and Rosenthal*) - 550*

Spleen. — Some points on the mechanism of filtration by the . . . (*Robinson*) - 568*

Spleen. — The . . . in West African yellow fever (*Klotz and Simpson*) 483

Spleen. — The . . . in West African yellow fever (*Klotz and Simpson*) 569*

Sympathicoblastoma. — The transformation of a malignant paravertebral . . . into a benign ganglioneuroma (*Cushing and Wolbach*) - 203

Sympathicotropic cells. — The . . . of the ovary and testis (*Brannan*) 343

Syngenesiotransplantation. — . . . in the guinea pig (*Loeb*) - - - - - - 29

Syngenesiotransplantation. — . . . in the rat (*Loeb*) - - - - - - - - - - 45

Synovial membrane origin. — Synoviomata: A histologic study of three tumors of . . . (*Smith*) - 557*

Synoviomata. — . . . (*Smith*) - 355

Synoviomata. — . . . : A histologic study of three tumors of synovial membrane origin (*Smith*) - 555*

Syphilitic aortitis. — The heart in . . . (*Clawson*) - - - - - - - - - - - - 575*

Syphilitic aortitis. — The involvement of the aortic valve in . . . (*Saphir and Scott*) - 527

Syphilitic aortitis. — The involvement of the aortic valve in . . . (*Saphir and Scott*) - 574*

T

Testis. — The sympathicotropic cells of the ovary and . . . (*Brannan*) 343

Thyroid extract. — A comparison in normal, thyroidectomized and hypophysectomized rats of the effects upon metabolism and growth resulting from daily injections of small amounts of . . . (*Smith, Greenwood and Foster*) - 669

Thyroid gland. — Studies on mitochondria. II. The occurrence of mitochondria-rich and mitochondria-poor cells in the . . . of man and animals (*Seecof*) - 365

Thyroid glands. — The effect of age of the host on the fate of transplants of . . . in guinea pigs (*Tureen*) - - - - - - - - - - - - - - - - - - - 501

Tongue. — Tuberculosis of the . . . with a case report (*Feldman*) - - - 241

Toxic production. — Studies of attenuation and of . . . of the diphtheria bacillus (*Wheeler*) - 540*

Toxic substance. — The absorption of the . . . of normal goat serum by guinea pig tissue (*Aronson*) - 539*

Tube. — Siphonic fermentation . . . for the more rapid isolation of the colon-typhoid group of organisms (*Jones*) - - - - - - - - - - - - - - 542*

Tubercle bacilli. — Additional experimental evidence of the intracellular distribution of . . . (*Haythorn*) - - - - - - - - - - - - - - - - - - - 566*

Tuberculosis. — Pulmonary blastomycosis; its similarity to . . . Report of two cases (*Medlar*) - 305

Tuberculosis. — Pulmonary blastomycosis; its similarity to . . . Report of two cases (*Medlar*) - 567*

Tuberculosis. — The reticulum of the lung. V. Its similarity in blastomycosis to that in . . . (*Miller*) - - - - - - - - - - - - - - - - - - - 315

Tuberculosis. — . . . of the tongue with a case report (*Feldman*) - - - - 241

Tuberculous lesion. — The reticulum of the lung. IV. Its presence in the reparative process of the . . . with and without caseation (*Miller*) 217

Tularemia. — . . . ,histopathology of the lesions in man (*Francis and Callender*) - 565*

Tumors. — The encapsulated . . . of the nervous system. (Meningeal fibroblasomas, perineurial fibroblastomas, and neurofibromas of von Recklinghausen) (*Penfield*) - 557*

Tumors. — Menstruating umbilical . . . (*Weller*) - - - - - - - - - - - - - 553*

Tumors. — Synoviomata: A histologic study of three . . . of synovial membrane origin (*Smith*) - 555*

U

Ulcer. — Pathologic changes in the nerves of the stomach wall in cases of chronic gastric . . . (*Okkels*) - 75

Umbilical. — Menstruating . . . tumors (*Weller*) - - - - - - - - - - - - - 553*

Uterus. — Adenocarcinoma of the . . . in a rabbit (*Rusk and Epstein*) 235

Uterus. — Tumor and foreign body giant cells in a fibrosarcoma of the . . . (*Mallory and Stewart*) - 85

V

Vagina. — Diffuse adenosis of . . . : a very rare disease (*Plaut*) - - - - 581*

Valve. — The involvement of the aortic . . . in syphilitic aortitis (*Saphir and Scott*) - 527

Vitamin content. — Local and systemic changes induced by lipoid solvents in animals fed on diets varying in . . . (*Jorstad and Johnston*) 489

W

Wassermann test. — A comparative study of basic beef heart antigens in the . . . (*Albray and Famulener*) - - - - - - - - - - - - - - - - - - - 539*

Y

Yellow fever. — The spleen in West African . . . (*Klotz and Simpson*) 483
Yellow fever. — The spleen in West African . . . (*Klotz and Simpson*) 569*

INDEX OF AUTHORS

INDEX OF AUTHORS

A

Abbott, Maude E. Coarctation of aorta (adult type) with complete obliteration of descending arch 572*

Albray, Marjorie C., and Famulener, L. W. A comparative study of basic beef heart antigens in the Wassermann test 539*

Anderson, John F., and Leonard, George F. Immunization of horses to erysipelas streptococcus toxin 541*

Arkin, Aaron. Periarteritis obsoleta nodosa. A study of the histologically healed end-stage 576*

——. Right-sided aorta (persistence of the right aortic arch) 572*

Aronson, J. D. The absorption of the toxic substance of normal goat serum by guinea pig tissue 539*

B

Baehr, George, and Rosenthal, Nathan. Malignant lymph follicle hyperplasia of spleen and lymph nodes 550*

Bell, E. T. Analysis of four hundred cases of primary hypertension . . . 578*

Bogin, Maxwell. See Smith and Bogin 67

Boyd, William. Pulmonary arteriosclerosis associated with primary carcinoma of the lung 574*

Brannan, Dorsey. The sympathicotropic cells of the ovary and testis . 343

Bronfenbrenner, J. The particulate nature of bacteriophage 561*

——, **Muckenfuss, R. S., and Hetler, D. M.** The study of intimate mechanism of the lysis of bacteria by bacteriophage 562*

Brunner, Matthew. Dermal testing as an aid to diagnosis of intestinal parasitic infestation 540*

Buck, L. W. See Rusk and Buck 568*

C

Callender, G. R., and Coupal, J. F. The first annual report of the registry of tumors of the lymphatic system 543*

——. See Francis and Callender 565*

Clawson, B. J. The heart in syphilitic aortitis 575*

Coleman, Marion B. See Gilbert and Coleman 542*

Coupal, J. F. See Callender and Coupal 543*

Covell, W. P. A quantitative study of the hypophysis of the human anencephalic fetus 17

* Abstract of paper presented at the meeting of the Association of Pathologists and Bacteriologists held at Rochester, N. Y., April 15 and 16, 1927.

Crawford, B. L., and Weiss, Edward. Three specimens of hearts showing congenital lesions 572*

Cushing, Harvey, and Wolbach, S. Burt. The transformation of a malignant paravertebral sympathicoblastoma into a benign ganglioneuroma 203

D

Davis, James E. The etiologic study of the pathology of eighteen congenital polycystic kidneys 570*

Dieckmann, Johanna M. See Gunn and Dieckmann 595

Dienes, L. Local hypersensitiveness. 539*

E

Epstein, Norman. See Rusk and Epstein 235

F

Famulener, L. W. See Albray and Famulener 539*

Feldman, Wm. H. Tuberculosis of the tongue with a case report . . . 241

Fisher, John H. Pyorrhea alveolaris: The rôle of certain microörganisms found in the lesions 169

Foot, Nathan Chandler. A case of primary mesenchymal hepatoma with necropsy 653

——. On the origin of reticulin fibrils 401

——. Studies on endothelial reactions. X. On the origin of the pulmonary "dust cell" 413

Foster, G. L. See Smith, Greenwood and Foster 669

Fox, Herbert. Experiments of two years on the relation of Hodgkin's disease and the organism isolated by Grumbach 544*

——. Intra-vital staining and phagocytosis in Hodgkin's disease, leukemia and sarcoma 546*

——. Relation of polynuclear neutrophiles and their reaction to X-ray, to certain lymphadenopathies 545*

Francis, Edward, and Callender, G. R. Tularemia, histopathology of the lesions in man 565*

G

Gardner, Leroy U., and Smith, David T. The origin of the alveolar phagocyte studied in paraffin sections of tissue stained supravitally with neutral red 445

—— **and Smith, David T.** The origin of the alveolar phagocyte studied in paraffin sections of tissue stained supravitally with neutral red . . 579*

Gettler, A. O., Rhoads, C. P., and Weiss, Soma. A contribution to the pathology of generalized argyria with a discussion of the fate of silver in the human body 631

Gilbert, Ruth, and Coleman, Marion B. The incidence of various species of bacteria in specimens of spinal fluid from cases of meningitis . . 542*

Goldblatt, Harry. See Steinberg and Goldblatt 541*

Goodpasture, Ernest W. Nuclear changes of ganglion cells in experimental herpetic encephalitis 395

—— **and King, Howard.** A cytologic study of molluscum contagiosum 385

Greenwood, C. F. See Smith, Greenwood and Foster 669

Gunn, Francis D., and Dieckmann, Johanna M. Malformations of the heart including two cases with common atrioventricular canal and septum defects and one with defect of the atrial septum (cor triloculare biventriculosum) 595

H

Haythorn, Samuel R. Additional experimental evidence of the intracellular distribution of tubercle bacilli 566*

Hetler, D. M. See Bronfenbrenner, Muckenfuss and Hetler 562*

J

Jackson, Henry, Jr. The histogenesis of urinary casts 285

Jacobs, William F. Malignant mediastinal dermoid with meningeal metastasis 556*

Jacobson, V. C., and Waddell, K. C. The effect of high voltage cathode rays on living tissue; an experimental study 560*

——. See Meyers and Jacobson 321

Johnston, Charles G. See Jorstad and Johnston 489

Jones, F. B. Siphonic fermentation tube for the more rapid isolation of the colon-typhoid group of organisms 542*

Jorstad, Louis H., and Johnston, Charles G. Local and systemic changes induced by lipoid solvents in animals fed on diets varying in vitamin content 489

K

King, Helen Dean. See Loeb and King 143

King, Howard. See Goodpasture and King 385

Kline, Gordon M. The demonstration of bacteriophage in old stock cultures 561*

Klotz, Oskar, and Simpson, Winifred. The spleen in West African yellow fever 483

—— **and ——.** The spleen in West African yellow fever 569*

L

Lambert, Samuel W. Sarcosporidial infection of the myocardium in man 663

Leonard, George F. See Anderson and Leonard 541*

Lewis, Paul A. The bacteriology of the blood of swine with particular reference to the virus of hog cholera 561*

Loeb, Leo. Syngenesiotransplantation in the guinea pig 29
——. Syngenesiotransplantation in the rat 45
—— **and King, Helen Dean.** Transplantation and individuality differential in strains of inbred rats 143
—— **and Wright, Sewall.** Transplantation and individuality differentials in inbred families of guinea pigs 251

M

MacNeal, Ward J., Otani, Sadao, and Patterson, Marjorie B. The finer vascular channels of the spleen 111
Mallory, F. B., and Parker, Frederic, Jr. Reticulum 515
—— **and** ——. Reticulum 553*
—— **and** ——. Spontaneous intracapillary glomerulonephritis in the rabbit 91
—— **and Stewart, Fred W.** Tumor and foreign body giant cells in a fibrosarcoma of the uterus 85
Marshall, Harry T., and Woodward, Katherine. Acute leukemia with extra medullary myeloid centers 547*
McCartney, J. S. Report of seventy-three cases of pulmonary embolism 572*
McGregor, Leone. A bloodless method for taking repeated blood pressure readings in laboratory animals 576*
Medlar, E. M. A report of two cases of essential adrenal insufficiency (Addison's disease) 135
——. Pulmonary blastomycosis; its similarity to tuberculosis. Report of two cases 305
——. Pulmonary blastomycosis; its similarity to tuberculosis. Report of two cases 567*
Meyers, Douw Schuyler, and Jacobson, Victor C. Multiple hemorrhagic sarcoma of Kaposi 321
Miles, W. L. See Rusk and Miles 289
Miller, William Snow. The reticulum of the lung. IV. Its presence in the reparative process of the tuberculous lesion with and without caseation 217
——. The reticulum of the lung. V. Its similarity in blastomycosis to that in tuberculosis 315
Muckenfuss, R. S. See Bronfenbrenner, Muckenfuss and Hetler . . . 562*

O

Okkels, Harald. Pathologic changes in the nerves of the stomach wall in cases of chronic gastric ulcer 75
Otani, Sadao. Studies on the islands of Langerhans in human pancreas. I. The relation of the islands to the surrounding structures 1
——. Studies on the islands of Langerhans in the human pancreas. II. Significance of variations in structure 123
——. See MacNeal, Otani and Patterson 111

P

Pappenheimer, Alwin M., and VonGlahn, William C. Studies in the pathology of rheumatic fever. Two cases presenting unusual cardiovascular lesions 583
Parker, Frederic, Jr. See Mallory and Parker 91
——. See Mallory and Parker 515
——. See Mallory and Parker 553*
Patterson, Marjorie B. See MacNeal, Otani and Patterson 111
Peabody, Francis W. The pathology of the bone marrow in pernicious anemia 179
Pederson, A. H. A method of producing experimental chronic hypertension in the rabbit 577*
Penfield, Wilder. The encapsulated tumors of the nervous system. (Meningeal fibroblastomas, perineurial fibroblastomas, and neurofibromas of von Recklinghausen) 557*
Plaut, Alfred. Diffuse adenosis of vagina: a very rare disease 581*

R

Rhoads, C. P. Vegetative endocarditis due to the meningococcus, with a case report 623
——. See Gettler, Rhoads and Weiss 631
Richter, Maurice N. Generalized reticular-cell sarcoma of lymph nodes, associated with lymphatic leukemia 547*
Robertson, H. E. A case of hypoglycemia, probably produced by a carcinoma of the islands of Langerhans 571*
Robinson, W. L. Some points on the mechanism of filtration by the spleen 568*
Rosenthal, Nathan. See Baehr and Rosenthal 550*
Rusk, G. Y., and Buck, L. W. Coccidioidal meningitis. 568*
—— **and Epstein, Norman.** Adenocarcinoma of the uterus in a rabbit 235
—— **and Miles, W. L.** Osteosclerotic anemia secondary to epidermoid carcinoma 289
——. See Smith and Rusk 225

S

Sampson, John A. Metastatic or embolic endometriosis, due to the menstrual dissemination of endometrial tissue into the venous circulation 93
Saphir, Otto. The state of the glomerulus in experimental hypertrophy of the kidneys of rabbits 329
—— **and Scott, R. W.** The involvement of the aortic valve in syphilitic aortitis 527
—— **and** ——. The involvement of the aortic valve in syphilitic aortitis 574*
Schultz, Oscar T. Diffuse lymphoma of mesentery associated with carcinoma of colon 549*

Scott, Ernest. Histological and chemical observations upon the origin of the polycystic liver 570*
Scott, R. W. See Saphir and Scott 527
——. See Saphir and Scott 574*
Seecof, David P. Studies on mitochondria. II. The occurrence of mitochondria-rich and mitochondria-poor cells in the thyroid gland of man and animals 365
Simonds, J. P. The organization of experimental adrenal cell emboli in the lungs 13
Simpson, Winifred. See Klotz and Simpson 483
——. See Klotz and Simpson 569*
Smith, Arthur H., and Bogin, Maxwell. Experimental gangrene produced by dietary means 67
Smith, Curtis E., and Rusk, G. Y. Pulmonary spirochetosis 225
Smith, David T. See Gardner and Smith 445
——. See Gardner and Smith 579*
Smith, Lawrence W. Synoviomata 355
——. Synoviomata. A histologic study of three tumors of synovial membrane origin 555*
Smith, Philip E., Greenwood, C. F., and Foster, G. L. A comparison in normal, thyroidectomized and hypophysectomized rats of the effects upon metabolism and growth resulting from daily injections of small amounts of thyroid extract 669
Steinberg, Bernhardt, and Goldblatt, Harry. Active immunization against experimental peritonitis 541*
Stewart, Fred W. See Mallory and Stewart 85

T

Tureen, Louis Leon. The effect of age of the host on the fate of transplants of thyroid glands in guinea pigs 501

V

VonGlahn, William C. See Pappenheimer and VonGlahn 583

W

Waddell, K. C. See Jacobson and Waddell 560*
Walzer, Matthew. Studies on the absorption of unaltered protein . . 539*
Warthin, Alfred S. The neoplastic relationship of Hodgkin's disease, aleukemic and leukemic lymphoblastomas and mycosis fungoides . 551*
Weiss, Edward. See Crawford and Weiss 572*
Weiss, Soma. See Gettler, Rhoads and Weiss 631
Weller, Carl V. Menstruating umbilical tumors 553*
Wheeler, Mary W. Studies of attenuation and of toxic production of the diphtheria bacillus 540*

Wolbach, S. Burt. See Cushing and Wolbach 203
Woodward, Katherine. See Marshall and Woodward 547*
Wright, Arthur William. Hyaline degeneration of the islands of Langerhans in non-diabetics 461
Wright, Sewall, See Loeb and Wright 251

Z

Zimmerman, H. M. A congenital anomaly of the heart: Truncus arteriosus communis 617